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Original Communications

DYSTOCIA IN DIABETES INSIPIDUS

THE RELATION OF PITUITARY OXYTOCIN TO PARTURITION

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THERE is general agreement in the literature that parturition can take place normally in the absence of the hypophysis. For example, Reynolds (1937), in his recent review article on the nature of uterine contractility, stated that no deficiency syndrome involving uterine activity has ever been described for the posterior pituitary lobe. Robson (1936) concluded that "The active changes occurring at parturition and leading to the expulsion of the fetus and placenta may take place in the absence of the pituitary (both anterior and posterior lobes), and in animals with inactive ovaries. Normal parturition may occur at a normal time in pregnancy in cases in which the activity of the pituitary can be excluded." Similarly, Van Dyke (1936), after reviewing the literature, concluded that the mechanism of labor was not under the control of the hypophysis.

During the course of an investigation on the relation of the so-called hypothalamico-hypophyseal system to diabetes insipidus, certain observations have been made which throw doubt on the conclusion that the hypophysis, and more especially its neural lobe, is not involved in parturition. It has been shown that experimental diabetes insipidus can be produced with great regularity in the cat and monkey by placing lesions in the anterior hypothalamus in such a position that they interrupt bilaterally the supraoptic component of the hypothalamico-hypophyseal tract (Fisher, Ingram and Ranson, 1935; Fisher, Ingram,

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Hare and Ranson, 1935; Ingram, Fisher and Ranson, 1936). The Horsley-Clarke stereotaxic instrument has been utilized in making the lesions described. For a detailed account of the findings on diabetes insipidus the reader should consult the monograph by Fisher, Ingram and Ranson (1938).

A brief description of the hypothalamico-hypophyseal system will be of assistance at this point. Fig. 1 is a diagrammatic representation of a mid-sagittal section through the hypothalamus and hypophysis of the cat. As can be seen the hypophysis has intimate topographic relations with the hypothalamus. Its neural division may be divided into 3 parts: the expanded portion or (1) *pars nervosa* is connected to the base of the hypothalamus by means of the (2) *infundibular stem* and the (3) *median eminence*. The latter is the rostral continuation of the ventral wall of the infundibular stem which forms a good part of the floor of the third ventricle. The glandular division is likewise composed of 3 parts: (1) the *pars tuberalis* which forms a cuff around the median eminence and the proximal part of the infundibular

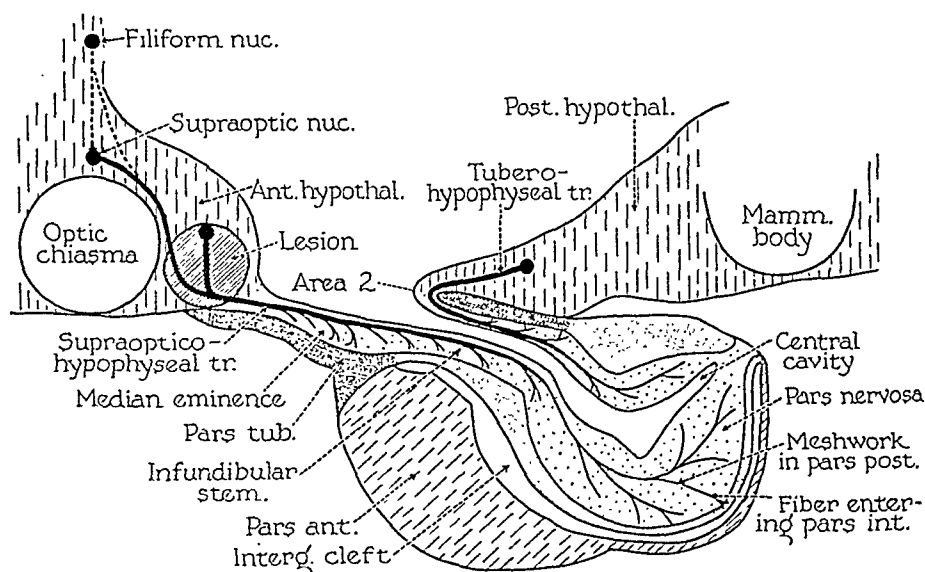


Fig. 1.—Diagrammatic representation of a medial sagittal section through the hypothalamus and hypophysis in the cat. From Fisher, Ingram, and Ranson: Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance, Edwards Brothers, Ann Arbor, Mich.)

stem; (2) the *pars intermedia* which completely invests the *pars nervosa* and is separated by the interglandular cleft from the main component of the glandular division, (3) the *pars anterior*. A heavy bundle of unmyelinated nerve fibers, the hypothalamico-hypophyseal tract, connects the neural division of the hypophysis with the hypothalamus. This tract has 2 components: (1) the supraoptico-hypophyseal tract arises mainly from the supraoptic nucleus and takes the path indicated in Fig. 1 to enter the median eminence, pass through the ventral wall of the infundibular stem and finally to spread out in a dense meshwork in the *pars nervosa*. (2) The tubero-hypophyseal tract arises from the lateral and caudal peri-infundibular regions and enters the dorsal wall of the infundibular stem. We would emphasize that all 3 parts of the neural division appear to have the same structure, although the median eminence and infundibular stem are somewhat specialized for the conduction of fibers to the *pars nervosa*.

The obliquely striped circle in Fig. 1 represents the location of a typical lesion designed to produce experimental diabetes insipidus. When such lesions are made the neural division of the hypophysis undergoes a series of striking degenerative changes, a detailed account of which will be found in the references given above. Briefly all 3 parts of the neural division show marked thinning and hypercellularity,

the unmyelinated nerve fibers degenerate and the specialized glial elements (pituicytes) disappear. An example of a degenerated and atrophic neural lobe from a cat with diabetes insipidus is shown in Fig. 3 which should be compared with Fig. 2; the latter represents a transverse section through the hypophysis of a normal cat.

It has been shown that the atrophic neural lobes from cats which develop diabetes insipidus, following interruption of the supraoptico-hypophyseal tracts, are markedly deficient in antidiuretic, pressor and, of great importance for the subject under discussion, oxytocic activity (Fisher and Ingram, 1936; Fisher, Ingram and Ranson, 1938). It has been concluded, therefore, that diabetes insipidus is essentially a deficiency syndrome caused by the failure of the atrophic neural division to secrete the antidiuretic hormone.

Diabetes insipidus has been produced in a large number of cats, 85 in all. Among these were 7 animals in various stages of pregnancy at the time of operation. All of these animals carried their litters to

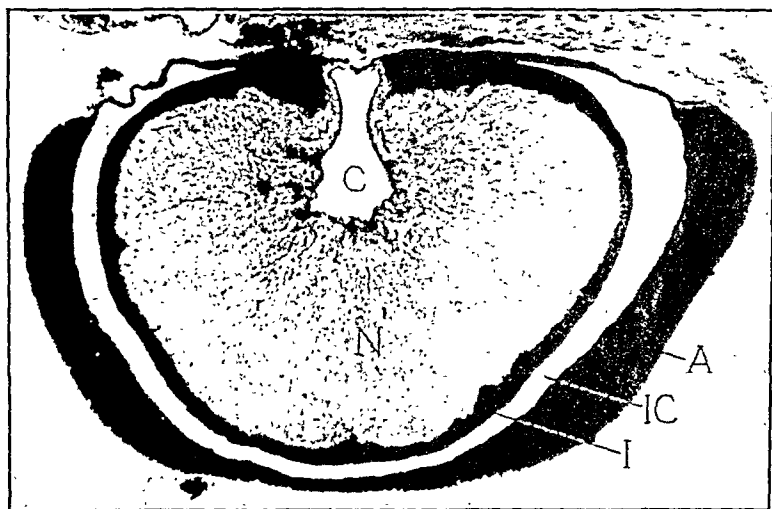


Fig. 2.—Enlarged photograph of a section through the hypophysis of a normal cat. A, pars anterior; C, central cavity; I, pars intermedia; IC, interglandular cleft; N, pars nervosa.

term but developed a striking disturbance of the delivery mechanism. Four of them died in the course of a greatly prolonged labor during which they were either totally unable to expel the uterine contents or else succeeded in delivering only a part of their young. Two of these animals have already been discussed briefly in a previous paper (Ingram and Fisher, 1937). Three of the 7 animals managed to survive parturition, but only after a protracted period of labor; 2 of these died within a few weeks after delivery. The implications of these results are of sufficient importance to warrant a more detailed discussion.

It will help to clarify the following summary of results if it is pointed out that after bilateral interruption of the supraoptico-hypophyseal tracts the resulting diabetes insipidus develops in several stages. Immediately following operation a temporary increase in the daily fluid exchange of varying proportions makes its appearance

and usually lasts for four or five days. This has been called the *transient phase* of diabetes insipidus. A period of normal water exchange, which has been designated the *normal interphase* then follows. In the majority of cases a persistent increase in the fluid exchange develops about two weeks postoperatively. This is the *permanent phase* of diabetes insipidus.

SUMMARY OF RESULTS

The permanent phase of the diabetes insipidus in the 7 cats under consideration commenced after latent periods varying from eleven to seventeen days. All the animals but one (D61) had well marked increases in the daily fluid exchange, varying from 3 to 10 times the normal. In one instance (D121) the fluid exchange frequently reached about a liter per day, the most severe case of diabetes insipidus we have seen. In Cat D61 only a mild increase in the fluid exchange was observed. Four of the cats were operated upon when pregnancy was about one-half advanced, two when it was two-thirds advanced and one a few days after impregnation.

Labor started in the different animals at periods varying from the nineteenth to the sixtieth postoperative days. In the cat, term is generally considered to be sixty-three days. Continuous observations were not made on these animals so that the precise duration of labor was not determined. However, the minimum time of labor can be calculated in 6 of them. Of these, 4 died in the midst of greatly protracted labors without delivering all their young. Cat D121 was in labor for about forty-eight hours during which time she delivered 4 kittens; 2 were retained and found in utero at autopsy. Cat NS67 died after a labor which lasted at least 12 hours without succeeding in delivering a single one of her 4 young. In a period of at least fifty-five hours Cat NS68 delivered 2 kittens; at autopsy 2 more were found in utero. The observations on Cat D61 were not complete but it is known that she died during the night after one partly delivered fetus was removed from the birth canal. The remaining 3 cats managed to survive parturition and delivered their full litters but only after prolonged labor. The minimum laboring time in Cat NS69 was twenty-nine hours during which 4 kittens were born. Cat NS40 was in labor about forty-eight hours and delivered 3 kittens. The shortest labor occurred in Cat NS66 and this animal was the only one of the series to survive parturition in good health and for a long period. The calculated minimum time of labor in this case was seven and one-half hours, but without doubt it was actually much longer than this since the animal was already in labor when first observed and since this calculation includes the time only up to 6 P.M. of the thirty-ninth postoperative day. The last-born kitten was delivered some time between 6 P.M. on the thirty-ninth day and 8 A.M. of the fortieth day.

In the cases of Cats D61, D121, NS67, and NS68 there can be no doubt about the disturbance of the delivery mechanism. But Cats NS40, NS66, and NS69 managed to survive parturition and the question arises whether labor lasted longer than normal in these instances. Accurate data on the duration of labor in the normal cat are difficult to find. We have seen one normal cat deliver 3 kittens in a period of less than two hours, and Cat NS35, to be discussed presently, gave birth to 3 kittens in a period of one hour. Dr. Windle informs us that he has recently observed a cat deliver 4 kittens in a two-hour period and another expelled 5 in a space of two and one-half hours. We believe, therefore, that Cat NS66 is the only animal of our series whose delivery time may possibly have been within the normal range, but it is more probable that it was prolonged.

There are several other points worth noting. Cats D121, NS67, NS68, and D61 died in the midst of labor. The cause of death was not determined but exhaustion and uterine sepsis probably played a role. All the kittens delivered were full term except for 2 mummified fetuses found in the uterus of Cat NS67. The 2 unborn kittens found in the upper ends of the uterine horns of Cat D121 were straightened to full length and firmly compressed. A similar stretched fetus was found in the

uterus of Cat NS67 and one in Cat NS68; in addition these last two fetuses had macerated skulls. These observations suggest that violent, perhaps uncoordinated uterine contractions had taken place. Five of the 6 cats on which we have observations showed good development of the mammary glands and lactation. Cat NS69 nursed her young for several days, but lactation stopped when the animal began to decline. Cat NS66 cared for and nursed her young for three weeks, and Cat NS40 for nine days.

Of the 3 cats which survived parturition, 2 (NS40 and NS69) gradually declined and were killed on the ninth and eighteenth post-partum days, respectively. Cat NS66 was the only one of the animals which remained in good health for a long period after parturition, and it was in this case that the duration of labor was the shortest.

A few observations are available which indicate that lesions in the hypothalamus, which do not cause diabetes insipidus, also do not interfere with parturition. Two cats were operated upon for diabetes insipidus but failed to develop it. Cat NS35 delivered 3 kittens within the space of an hour on the thirty-fourth postoperative day. She remained in good health and nursed her young. About two weeks post



Fig. 3.—Enlarged photograph of a section through the hypophysis of a cat with diabetes insipidus, showing atrophy of the pars nervosa and enlargement of the central cavity. (See legends for Fig. 2 for explanation of lettering.)

partum she came into heat and was mated. Cat NS33 delivered 2 normal full-term kittens on the twenty-first postoperative day. They were born some time between 6 P.M. of one day and 9 A.M. of the next, but the exact duration of labor was not ascertained. The mother nursed the kittens. About a month post-partum she came into heat and was bred. In these 2 cases there was probably partial destruction of the supraoptico-hypophyseal system. Another animal with moderate destruction of the supraoptico-hypophyseal system insufficient to cause diabetes insipidus delivered 3 kittens, which she nursed until they were weaned. A fourth animal with hypothalamic lesions, the location of which was not checked, was bred and delivered 5 kittens which she nursed until weaned. The exact duration of labor in these last 2 cases was not determined, but we know that it was not unduly prolonged.

The hypothalamico-hypophyseal region of Cats D61, D121, and NS67 has been examined in serial sections. In all 3 of these cases the lesions were found in a position to interrupt the supraoptico-hypophyseal tracts. For a detailed description of the lesions and the accompanying degenerative changes in the hypothalamico-hypophyseal system found in animals with diabetes insipidus, the reader is referred to the monograph by Fisher, Ingram and Ranson (1938). A transverse section through the markedly atrophic pars nervosa of Cat D121 is shown in Fig. 3.

DISCUSSION

The obvious explanation for the disturbance of the delivery mechanism in these animals is that they have a deficiency in the amount of pituitary oxytocic hormone. It has been shown that the atrophic neural lobes of cats with diabetes insipidus show little or no oxytocic activity and all of these 7 animals had this disorder (Fisher and Ingram, 1936; Fisher, Ingram and Ranson, 1938). Thus, it was found that 3 normal hypophyses contained 2.5, 3.5, and 2.2 oxytocic units, respectively, while 4 atrophic glands had in each instance less than 0.25 units. Further, the atrophic glands of Cats NS67, NS68, and NS69 have been assayed for their antidiuretic activity. The gland of Cat NS68 was entirely inactive while NS67 and NS69 contained 0.06 and 0.04 antidiuretic units, respectively. Without doubt these glands would have shown a deficiency in oxytocic activity had they been tested.

The degeneration of the hypothalamico-hypophyseal system in these cats and the consequent diminution in the hormone content of the neural division seem to be the only pathology present which could account for the disturbance in parturition. The pars anterior has been found to be normal, or at most only slightly subnormal, in function in animals with diabetes insipidus. This is shown by the integrity of the gonads, thyroids and adrenals in the great majority of instances, by the continuation of growth in young animals and, as we believe, by the development of the permanent phase of the diabetes insipidus itself. The fact that at least 5 of the pregnant cats lactated is further evidence for the presence of pars anterior function (Nelson, 1936).

Although gross atrophy of the ovaries does not appear to develop in diabetic cats, it is possible that there is some abnormality of ovarian function in these animals. We have never observed any of them to come into heat so that pregnancy has never occurred after the diabetes became established. It is doubtful, however, whether a possible disturbance of ovarian function could be related to the abnormal parturition which has been described. Robson (1936) states that parturition can take place in the presence of inactive ovaries and it is well known that pregnancy will continue in women after oophorectomy, and delivery will be perfectly normal.

We hesitate to state positively that the disturbance in parturition which we have observed represents an oxytocic deficiency symptom because our series of animals was not large and our observations conflict with those of previous investigators. It will be well, however, to briefly review the literature on the relation of the hypophysis to parturition to ascertain on just what evidence the oxytocic hormone has so generally been rejected as a factor influencing the mechanism of delivery. It is our opinion that the results so far recorded in the literature do not warrant such rejection, that they have been interpreted uncritically and many of the experiments have been inadequately controlled. The whole problem requires further experimentation and should be thrown open for reconsideration. It may well turn out that the oxytocic hormone of the neural division, like the anti-

diuretic hormone, has an actual physiologic function and is something more than an interesting pharmacologic artefact; it is, after all, one of the most potent uterus-contracting substances known.

In attacking this problem experimentally the natural thing to do is to remove the neural division of the hypophysis or bring about its degeneration, determining subsequently the effect upon parturition. Actually this procedure has been followed by previous investigators in only a few instances. In most cases the entire hypophysis has been extirpated. There are 2 other factors which should be taken into consideration in evaluating the evidence on this subject. First, an adequate histologic examination of the hypophyseal region must be an absolute prerequisite to the acceptance of any conclusions drawn from extirpation experiments. For it has been our experience that the presence of remnants of the median eminence and infundibular stem usually prevents the development of the permanent phase of diabetes insipidus and may likewise permit of normal parturition. It has been emphasized that the 3 parts of the neural division of the hypophysis, namely, the median eminence, infundibular stem and pars nervosa, represent an anatomic unit and it appears probable that they act also as a functional unit. Second, some statement as to the duration of labor should be demanded.

On the basis of one or another of the above criticisms the work of the following investigators must be accepted with some caution. Allan and Wiles (1932), McPhail (1935a), Pencharz and Lyons (1933-1934), Selye, Collip and Thomson (1933-1934), McPhail (1935b) and Firor (1933).

Smith (1932) is the only investigator who has specifically studied the effect of isolated posterior lobe removal on parturition, and his work has been widely quoted as proving the nonessentiality of the posterior lobe in parturition. It should be pointed out that Smith expressly stated that the infundibular stem and pars tuberalis were left intact in his small series of 6 rats and, therefore, the extirpation of the neural division cannot be said to have been complete. Further, no statement was given as to the duration of labor in comparison with normal rats.

Keller and Hamilton (1937) reported the case of a dog with diabetes insipidus following section of the infundibular stem which bred and delivered a litter of 3 pups at term, but no data were given as to the duration of labor.

In spite of statements to the contrary, disturbances of the mechanism of parturition following hypophysectomy have been observed by other investigators which appear to resemble very closely those which we have observed. The most extensive investigation is that of Pencharz and Long (1933). In a series of 28 rats hypophysectomized from the eleventh to the twentieth days of pregnancy a marked derangement of the birth mechanism was observed. This disturbance took one of two forms: either the mother died at the end of a prolonged period of gestation (three or four days past term) without delivering her young or the birth of dead and living young occurred after a similarly prolonged period of pregnancy. As in our cats, macerated and greatly elongated fetuses were found in utero.

Pencharz and Long believed that the derangement of the birth mechanism which they observed was due to the removal of the pars anterior and not to the absence of the neural division. In only a few instances did they make serial sections of the brain base and the pituitary, the completeness of the operation at autopsy being checked in most cases by examining the hypophyseal region under a dissecting binocular. They concluded that the disturbance of parturition appeared only when the pars anterior was reduced to approximately one-fourth of the entire gland. In the absence of a microscopic examination it may reasonably be maintained that in those cases where larger remnants of the pars anterior were left intact greater portions of the neural division likewise escaped extirpation, and that it was this rather than the presence of more pars anterior tissue which prevented the development of the disturbance of parturition.

The results of Pencharz and Long have been duplicated by Selye, Collip and Thomson (1932-1933) and by Bergman (1934a, b), both working on the rat. In neither case was there a microscopic report.

We are not here concerned with the complex matter of the mechanism of labor except to point out that the demonstration that pituitary oxytocin plays a role in those changes which lead to the expulsion of the fetuses at parturition does not conflict with the prevailing theories of the mechanism of labor. In fact, such a demonstration would lend support to these theories and supply one important missing link. Marrian and Newton (1935) have pointed out that there is a considerable body of opinion in favor of the view that labor is determined by a critical concentration of two or more hormones being simultaneously achieved. For instance, that under the influence of increasing amounts of estrin the uterus becomes more and more sensitive to oxytocin with the advance of pregnancy until the threshold concentration is reached. One major stumbling block to the estrin-oxytocin synergism theory is the fact that the hypophyseal extirpation experiments reviewed above have been generally interpreted as excluding oxytocin from the process of parturition. For this reason Marrian and Newton suggest that there may be an extrahypophyseal source of oxytocin, and Bell and Robson (1937) have considered the possibility that the fetal pituitary may supply oxytocic hormone which passes into the maternal circulation and influences the process of parturition.

Finally, we would like to refer to a recent article by Newton (1937) on the insensitivity of the cervix uteri to oxytocin. This author points out that if evidence is ever brought forward proving that the oxytocic principle is involved in parturition, "it must take account of the fact that mere contraction of the uterus is too primitive a process to be dignified by the name of parturition: it is impossible, for instance, to visualize the delivery of the fetuses, five in each horn of the uterus, without some coordinating mechanism. It is not necessary to endow the oxytocic principle itself with any coordinating function, for the type of muscular activity might be determined by some other factor, the oxytocic principle serving merely to potentiate the contractions. It is, on the other hand, necessary to postulate that this should not cause incoordinated movements." The most severe type

of incoordination, according to Newton, would be a simultaneous contraction of the cervix and cornua of the uterus, for this would prevent the expulsion of the fetuses. It appears, however, that such simultaneous contraction does not take place, for Newton was able to demonstrate that in the rat and guinea pig, in any phase of sexual activity, the cervix uteri does not react *in vitro* to large doses of Pitocin. The conclusion was drawn that the oxytocic principle still cannot be excluded from the factors responsible for parturition.

SUMMARY

Observations have been presented on 7 cats in which experimental diabetes insipidus was produced during various stages of pregnancy by making appropriate lesions in the hypothalamus. It was shown that these animals developed striking disturbances of the mechanism of parturition during which they were totally or partially unable to deliver their young or else succeeded in doing this only after a greatly prolonged labor which lasted in some cases over two days. Four of the cats died in the midst of labor; 2 survived for some days but finally succumbed; only one remained alive and in good condition.

These findings were discussed in relation to the theory that the disturbance noted was due to a deficiency in pituitary oxytocic hormone consequent upon interruption of the hypothalamico-hypophyseal tract. A critical analysis of the literature covering the effect of hypophyseal ablation on the delivery mechanism was presented. It was concluded that the work so far reported does not warrant the rejection of pituitary oxytocin as a factor involved in normal parturition, and the suggestion was made that the problem should be thrown open for further investigation.

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THE HISTOLOGIC CORRELATIONSHIP OF ENDOMETRIAL AND CERVICAL BIOPSIES

WITH COMMENTS ON THE ETIOLOGY OF ENDOCERVICITIS

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RECENT advances in gynecologic endocrinology, notably the isolation of the two ovarian hormones, and the experimental proof of their respective physiologic effects on the structure of the mucous membranes, gave a new impetus to research work on the endometrium. Experimental observations on animals and castrated women furnish conclusive evidence that estrogen, the hormone of the growing and ripe follicle causes proliferation in the endometrium, and that its prolonged and continuous action produces glandular hyperplasia in this structure. The corpus luteum hormone, progesterin, on the other hand, causes certain cytologic changes in the epithelial elements, the manifestation of which is the secretory function.

Since the physiological effects of the actions of both ovarian hormones were clearly defined, attempts have been made to interpret histologic findings in the endometrium on the basis of the recent explanations of hormonal activity. It seems logical that if the specific hormonal effect on the mucous membranes is known, a careful interpretation of the histologic picture may disclose the status of hormonal balance in the ovaries. There being no rest period in ovarian function, the hormone balance is a constantly changing process, and consequently the mucous membranes of the genital tract must undergo a continuous structural change. It is evident that the histologic study of a single specimen, obtained from the mucous membranes at any one phase of the menstrual cycle, cannot be utilized for a reconstruction of the ovarian mechanism. To judge an individual's endocrine make-up on the basis of the ever-changing balance of the ovarian hormones, it is necessary that several biopsies be obtained during one intermenstrual period. A comparative study of such specimens may reveal the true picture of the ovarian mechanism, which seems to be a highly individual and intricate process.

Various ingenious methods were devised to obtain endometrial fragments for microscopic examination, but none of these procedures makes an intensive and reliable periodic investigation of the menstrual cycle feasible. The amount of tissue obtained by suction or punch biopsies is often insufficient for a conclusive diagnosis of the menstrual phase in the endometrium. It must be remembered that the histologic cycle of the endometrium is not a uniform and synchronous tissue change. Rock and Bartlett¹ rightly emphasize the importance of getting the endometrial biopsies from high on the anterior or posterior walls of the uterus, be-

cause only there are the cytologic changes complete. It is obvious that a comparative study of subsequent biopsies taken from different levels of the lining membranes will lead to misinterpretations. The selection of proper areas within the uterine cavity is difficult, and to obtain four or five subsequent specimens in one intermenstrual period from the same level of a surface, not yet denuded of endometrium, is well nigh impossible. Furthermore, clinical observations prove that repeated intrauterine manipulations have a disturbing effect on the normal menstrual cycle. Previously normally menstruating women are prone to show irregularities of their menstrual dates after such procedures. These temporary disturbances of the normal hormonal set-up, the cause of which is unknown, may also result in misinterpretations. In addition to these fundamental disadvantages of periodic endometrial biopsy methods, it also remains questionable whether a sufficiently large number of women can be induced to submit to weekly intrauterine manipulations for diagnostic purposes. It is a painful procedure which cannot always be carried out without some form of anesthesia, and it is not unlikely that its universal application may eventually result in serious aftereffects in some cases, as a result of traumatization or infectious processes.

A tissue index other than the endometrium is available in the human being; a histologic structure, which is easily accessible, which permits a periodic study by simple and safe methods, and which furnishes reliable evidence of the ovarian activity. The results of my investigations^{2, 3} of the cervical mucosa indicate that this histologic structure may be the test object which fulfills all the requirements. In my previous publications^{2, 3} I described the method used for obtaining cervical tissue specimens for histologic study, and reported my observations on the cyclic changes in this tissue. In my hands the cervical biopsy method proved to be safe, simple, and reliable. It is essential that a 3 to 4 mm. wide strip should be removed from the entire length of the cervical canal. The circular surface of the endocervix offers a large enough area for taking four or five such specimens at weekly intervals. The re-epithelization of the denuded surface progresses rapidly, and three weeks after the removal of the last specimen a perfectly normal looking cervix can be visualized through the speculum. In my cases no inflammatory reaction followed excision, normal menstruation was not disturbed, and all my patients menstruated at the expected time and continued to have normal periods thereafter.

The demonstration of a histologic cycle in the cervical mucosa, which I reported in a previous paper, did not conclusively prove its interdependence with the ovarian cycle. It therefore became my purpose in the present study to investigate the relationship between changes found in the cervical mucosa and the known effects of ovarian hormone activity. A direct method of studying the ovarian cycle in the human being not being practicable, I selected an indirect way, by undertaking a comparative histologic study of the endometrium and cervical mucosa, both specimens being removed from the same individual at the same time. The histologic effects of the ovarian hormones on the endometrium are so well established that the cytologic changes in this structure constitute

a reliable basis for the determination of the cervical mucosa's corresponding participation in the ovarian cycle.

All together, 44 women were studied in this series. Since it was necessary to obtain liberal amounts of endometrial tissue for the desired purposes, it seemed wise to secure them by means of dilatation and curettage under gas anesthesia. Immediately after removing the endometrial specimen, an approximately 4 mm. wide strip was excised from the entire length of the cervical canal.

All of the patients had normal menstrual histories and normal pelvic organs. Their ages varied from 26 to 43 years. Only 35 of the 44 could be utilized for the purposes of this study, because, notwithstanding the curettage, the endometrial tissue obtained proved insufficient to justify a positive diagnosis. It seems that normal endometria cannot always be readily obtained, even by curettage, particularly in the early proliferative phase of the cycle. On the other hand, no such difficulty is experienced with the cervical biopsy method, as it is always easy to remove the desired amount of tissue by means of the cutting current.

In the 35 cases, in which both specimens could be adequately studied, the entire span of the intermenstrual period was represented. On two days, the fourteenth and sixteenth after the beginning of the previous menstruation, only one case each came under observation; on all of the other days, two or more cases were available for investigation.

The histologic features of the endometrial cycle on the basis of recent endocrine knowledge have been clearly elucidated by various authors (Burch,⁴ Campbell and others,⁵ Herrell and Broders,⁶ and Rock and Bartlett¹) but the arbitrary division of the intermenstrual period into different phases is still under discussion. In accordance with the ovarian hormone action, the influence of which governs the histologic changes, the intermenstrual period may be divided into two phases: (1) estrin phase and (2) estrin, corpus luteum phase. Due to the progressive changes in both of these phases a subdivision into, (a) early proliferative, (b) late proliferative, (c) early secretory, and (d) late secretory phases is practical from a histologic standpoint. Since the hormonal action is continuous and progressive, a constant change takes place in the mucous membranes, which is neither uniform nor synchronous, and therefore time limits for the different phases are necessarily theoretical and not always substantiated by microscopic observations.

The endometrial changes in the estrin phase are characterized by frequent mitoses, the glandular elements increasing in number and size. The epithelial cells, which at first are distinctly cuboidal or low columnar become gradually higher, and at the peak of estrin production become ill-defined, bulging, crowded, and irregular. The nuclei of the cells also undergo a change. They are deeply stained, oval-shaped, and basally arranged in the early proliferative stage, and later become elongated, spindle-shaped, pale, and centrally migrating bodies. The stroma changes from a dense, fibrous tissue with collapsed blood vessels into a highly edematous, cellular, engorged structure. The corpus luteum hormone has a qualitative influence on the cells, which manifests itself in secretory activity.

In a previous paper, I demonstrated that the cervical mucosa undergoes much the same change as the endometrium, and this statement is corroborated by the results of the present investigation.

I classified the specimens in the following four menstrual groups: (1) early proliferative, (2) late proliferative, (3) early secretory, and (4) late secretory. The comparative study of the endometrial and cervical biopsies revealed a synchronous hormonal action in both structures, but the histologic picture failed to correspond with the known menstrual dates in all cases. In three of them a discrepancy was found between the histologic findings and the clinical history of menstruation. One of these cases is worthy of special mention. The patient was 26 years old, had always menstruated regularly, and had normal pelvic organs. Endometrial and cervical specimens were obtained on the twenty-third day after the first day of her last menstruation. The microscopic picture of the endometrium was characteristic of beginning late proliferation, but the histology of the cervical specimen corresponded exactly with the clinical menstrual date. So in this instance the histologic study of the cervical mucosa gave a more accurate diagnosis of the cyclic phase than did the endometrium. A possible explanation of this discrepancy between endometrial and cervical findings may be that the endometrial specimen was secured from an area of the uterine lining which was not representative of the cyclic phase, and in which the cytologic transformation was not complete. This observation seems to indicate that endometrial biopsies, even if obtained by curettage, cannot always be relied upon from an endocrinologic diagnostic standpoint.

The appended brief histories, with histologic findings and photomicrographs illustrating the specimens, are typical examples of each menstrual phase.

CASE 1.—A 37-year-old woman, married twelve years. Had two children: 8 and 5 years old. Normal deliveries. Had one miscarriage four months ago. Menstrual history normal, usually of four days' duration; last period: May 1 to 5. Endometrial and cervical biopsies were taken on May 7.

Study of the endometrium revealed the following: The glands were stretched with small lumina and were lined by a single layer of low columnar epithelium. The individual cells were well defined and showed relatively little cytoplasm. The nuclei were oval and had a basal arrangement. There were a conspicuous number of typical mitoses. The interglandular stroma was dense, the cells showing deep staining nuclei with little cytoplasm. There were scattered lymphocytes and a few leucocytes in the stroma.

The cervical biopsy specimen showed the following histologic picture: the surface was covered by moderately high columnar epithelium with deeply stained, oval-shaped nuclei, showing a basal arrangement. The individual epithelial cells were sharply defined and formed a continuous layer on the surface. The glands were scanty with narrow lumina and devoid of secretion. The lining consisted of a single layer of low columnar epithelium, the nuclei were deeply stained, oval shaped, and situated near the basal membrane. The stroma was dense, fibrous tissue, the cells having small deeply stained nuclei with inconspicuous cytoplasm. The vessels were collapsed.

Fig. 1 was a high power photomicrograph of the endometrial, Fig. 2 of the cervical biopsy of this case.

CASE 2.—A 39-year-old woman, married nineteen years. Had five children, the last one, two and a half years ago. She had had several miscarriages, the last

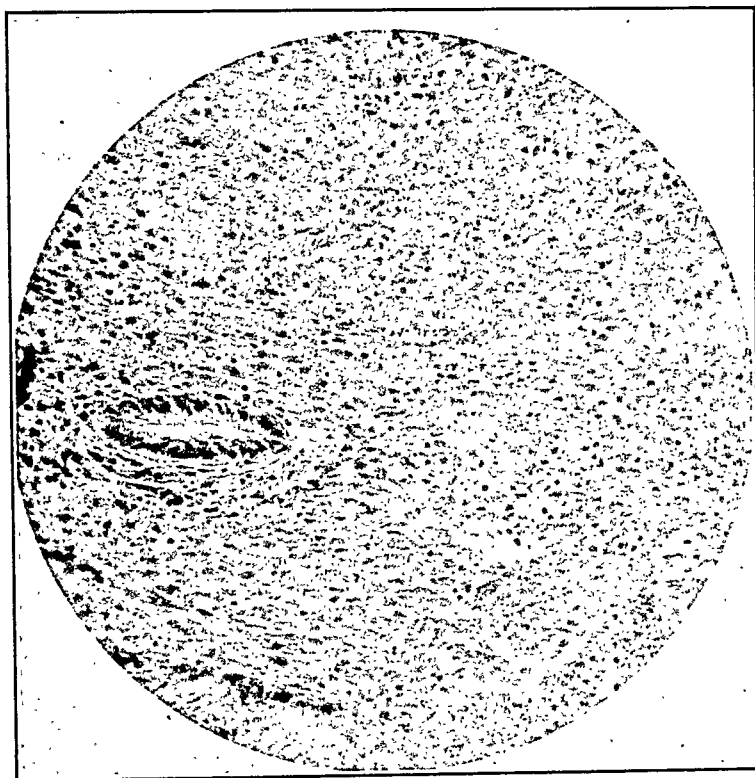


Fig. 1.—Endometrium of the early proliferative phase.

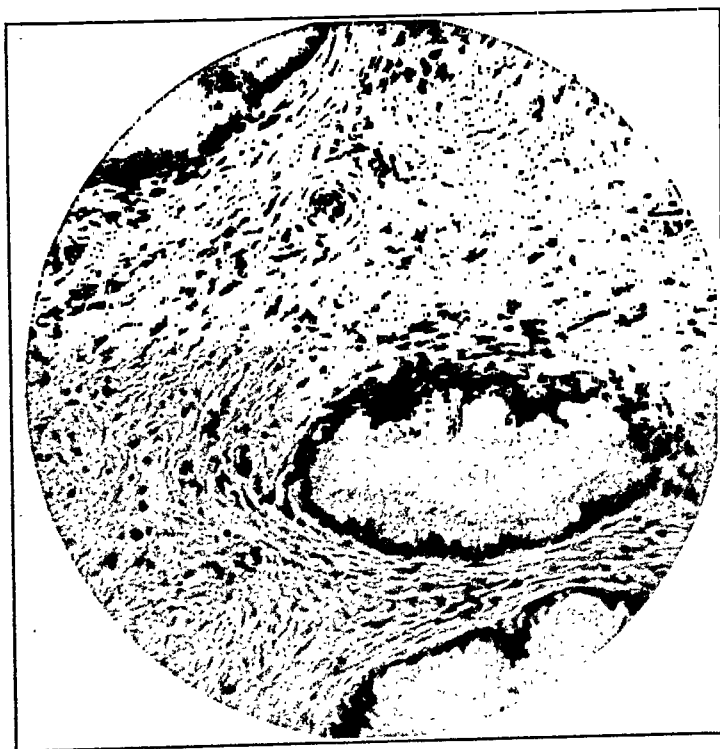


Fig. 2.—Endocervix of the early proliferative phase.

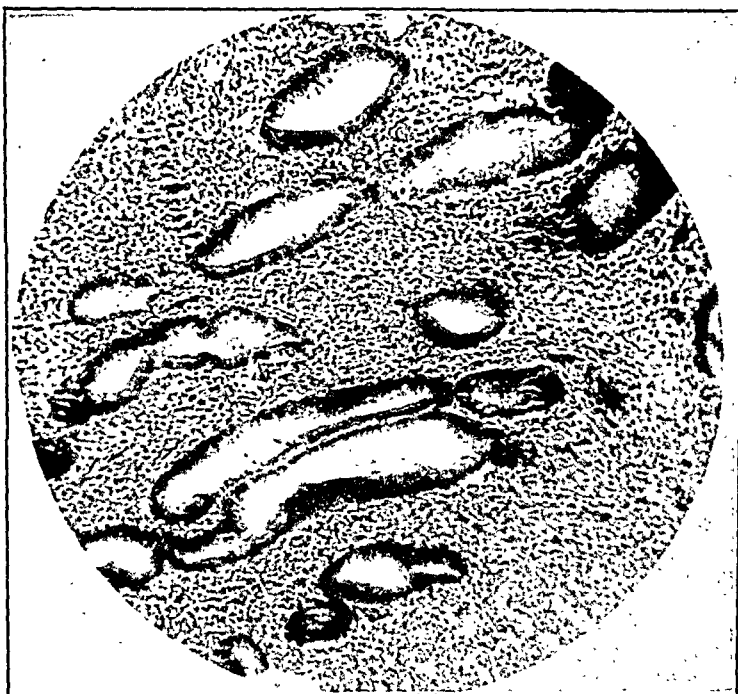


Fig. 3.—Endometrium of the late proliferative phase.

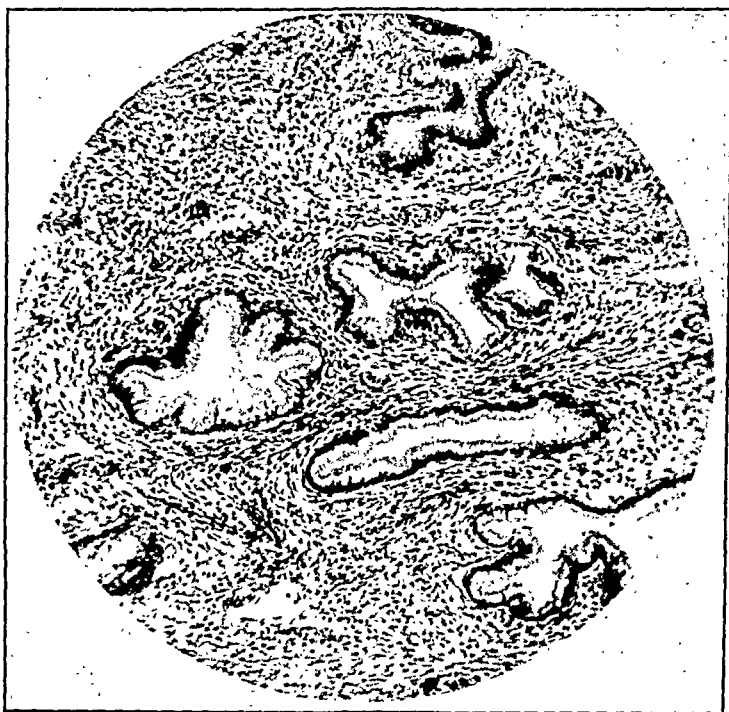


Fig. 4.—Endocervix of the late proliferative phase.

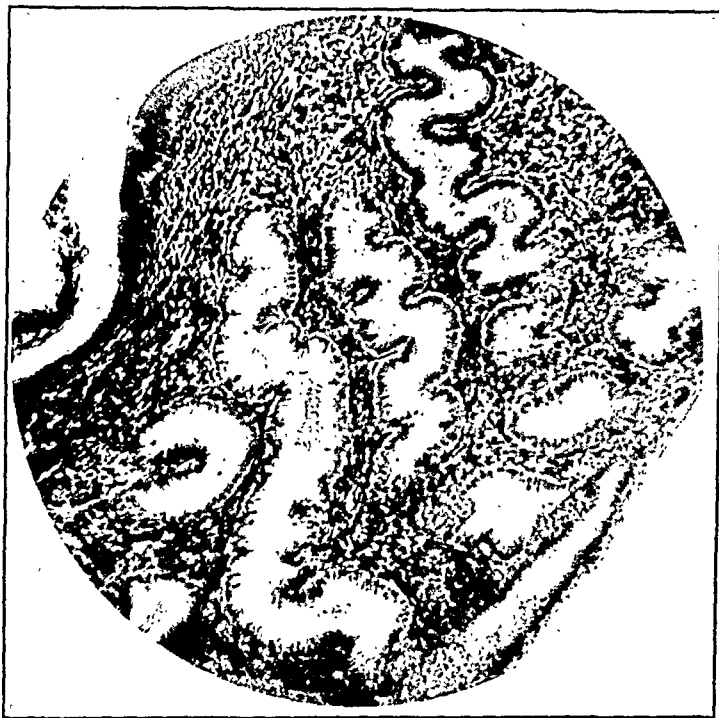


Fig. 5.—Endometrium of the early secretory phase.



Fig. 6.—Endocervix of the early secretory phase.



Fig. 7.—Endometrium of the late secretory phase.

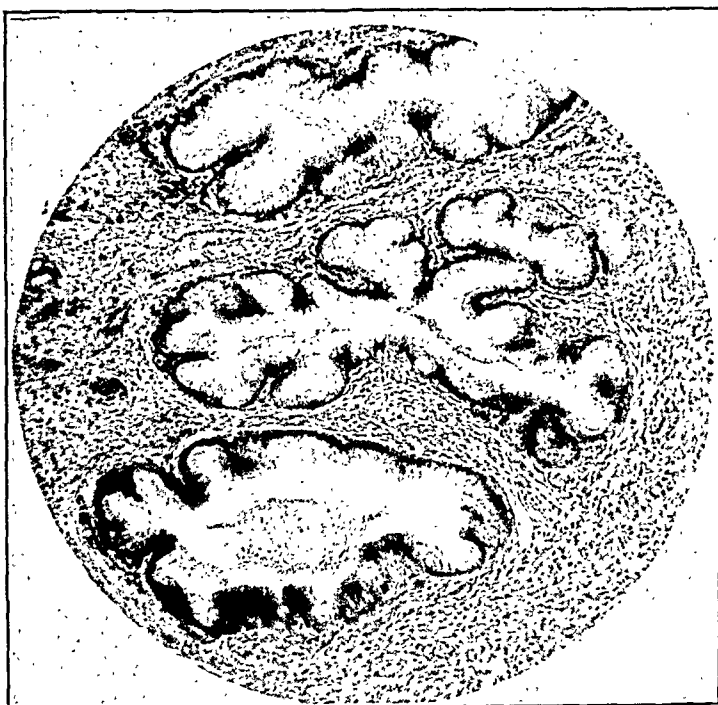


Fig. 8.—Endocervix of the late secretory phase.

one five years ago. She menstruated every twenty-eight to thirty days, three days' duration, of moderate amount. Last period: January 29 to 31. The biopsies were taken on February 9.

Endometrial findings: The glands were slightly wavy and lined by a single layer of high columnar epithelium. The nuclei were somewhat elongated and close to the basal membrane. There were occasional mitotic figures. The interglandular stroma had small nuclei with little cytoplasm. There were areas, however, in which the stroma cells were large with pale stained nuclei. Scattered lymphocytes could be seen.

The cervical tissue: The surface was covered by a continuous layer of high columnar epithelium with oval shaped nuclei, which were deeply stained and which lay near the basal membrane. The glands were few, widely separated, and their epithelium was similar in every respect to the covering epithelium. The individual cells were well defined. The interglandular stroma was moderately cellular.

Fig. 3 demonstrates the endometrial, Fig. 4 the cervical specimen in this case.

CASE 3.—23-year-old woman, married six years. Had had one child six years ago. Menstruation occurred every twenty-eight days, four to five days' duration, moderate amount. Last period: April 20. Biopsies were taken on May 13.

Endometrial findings: The glands were tortuous and moderately dilated. The lining epithelium was high columnar. The nuclei were swollen and had a basal arrangement. The cytoplasm showed vacuolization in many places. The cells of the stroma were slightly swollen and near the surface they were separated by edema. The arterioles were prominent.

Cervical findings: The glands were numerous and presented a great variety of shape and form. Numerous projections into the lumen were seen. The lining epithelium was high with conspicuous cytoplasm. The nuclei were elongated and migrated to the center of the cell. The stroma was edematous and the vessels were prominent.

Fig. 5 shows the endometrial specimen and Fig. 6 the cervical specimen in this case.

CASE 4.—A 38-year-old woman, married fifteen years. Had had two children, the last one eight years ago. Four miscarriages, the last one five years ago. Menstruation occurred regularly every twenty-eight days, and was of six days' duration. Last period: December 17 to 23. Biopsies were taken on January 12.

Endometrial findings: The glands were markedly dilated and the lining epithelium revealed highly vacuolized columnar cells. The stroma cells were large with large pale nuclei and much cytoplasm. Among the stroma cells there were many lymphocytes. The arterioles were prominent and had thick walls: the capillaries were dilated and filled with erythrocytes.

Cervical findings: Numerous glands which were widely dilated and filled with mucus. The lining epithelium was high columnar; the cells were ill defined and bulged into the lumen. The basal arrangement of the nuclei was indistinct. The stroma revealed increased cellularity and prominent thick-walled arterioles.

Fig. 7 represents the endometrial, Fig. 8 the cervical specimen in this case.

DISCUSSION

A comparative histologic study of endometrial and cervical biopsies, taken from normally menstruating women with apparently normal genital organs, revealed identical and synchronous cyclic changes in both structures. The histologic effects of the ovarian hormones can be demonstrated as clearly in the mucosa of the uterine cervix as in the endometrium. In the study of the histologic cycle in human beings, the periodic cervical biopsy method offers distinct advantages over the endometrial biopsy procedures. These advantages are: (1) it always

is possible to obtain the desired amount of tissue for histologic study; (2) the specimens always comprising the entire length of the endocervix, a comparative study of subsequent biopsies is based on findings of identical structures of the mucous membranes; (3) the site of previous excisions is visible, which makes the selection of intact surfaces possible; (4) the histologic interpretation is facilitated by the fact that a compact piece of tissue is obtained, in which the different structural elements are found side by side, as they actually exist in situ; (5) the periodic cervical biopsy method can be carried out at weekly intervals as an office procedure, without anesthesia; (6) the regularity of menstruation is not affected.

I believe that the use of the cervical mucosa as a test-object will make possible an intensive study of the sex cycle in the human being. Definite knowledge of a histologic cycle in the endocervix is bound to change the interpretations of certain pathologic findings in this particular structure. Inflammatory diseases of the cervix are frequently diagnosed. Such a diagnosis may be based on histologic findings, or more commonly on the presence of clinical symptoms, of which an increased discharge from the cervical canal is regarded as most significant. The etiology of endocervicitis is often obscure, especially in young girls who are still virgins and who have no history of infection.

The histologic features of different types of endocervicitis were reviewed recently by Goodall and Power⁷ in a concise manner. Among other things, they stated that: "In the mild form of chronic endocervicitis an increased activity of the surface columnar epithelium is present. The hypersecretive type of cervicitis is characterized by columnar cells having a ragged free margin, expelling huge quantities of mucus. The nucleus moves away from the base of the cell, and it may occasionally ascend as far as the middle, leaving a clear space underneath it. The nucleus does not stain deeply. In the more advanced and intense chronic infections the state of hyperfunction may cause a complete explosion of the secreting cells with or without attempts at repair in the deepest basal membrane. In still other more acute stages, a wholesale blight may affect all the columnar cells, causing them to be cast off in a state of partial disintegration, not only of the surface, but of all the deeper glands. Secretion is not a prominent feature of this stage, rather destruction captures the attention. In hyperplastic types hyperplasia of the glandular linings is the predominant feature. In many instances a heaping up of tissue is observed, in which secretory function is partially or totally lost and cell energy seems to spend itself chiefly in division. The columnar cells lose their columnar mucus-secreting characteristics. The underlying stroma is usually but slightly affected by the infection. In acute interstitial cervicitis diffuse round cell infiltration of the deep tissues is present. Thrombophlebitic changes are frequent and consequent diapedesis or large venous hemorrhages do occur. Cystic disease of the glands usually occurs only in the chronic state."

In the course of my periodic cervical studies, I observed all of these supposedly inflammatory pictures at one or another phase of the histologic cycle and found them to be the characteristic manifestations of this structure's physiologic function. These changes were not of a permanent nature, but were found as different stages in the cyclic transformation of the endocervix. Increased activity of the columnar cells with mucus production and migrations of the nuclei is always observed in the secretory phase of the cycle. Exfoliation of the epithelium on the surface

and in the glands is physiologic shortly before and during menstruation. The heaping up of columnar cells with frequent divisions is present in the proliferative stage. Round cell infiltration and edema of the stroma with occasional diapedesis occur in the late secretory phase.

The present study not only yielded further evidence of the correctness of these observations, but also revealed that all these physiologic changes are not confined to the cervix alone, but are synchronous with similar changes in the endometrium. I therefore feel warranted in suggesting that physiologic phases of the histologic cycle may be erroneously interpreted as inflammatory reactions in the cervical mucosa.

The evaluation of an increased amount of discharge from the cervical canal as an expression of inflammatory involvements also requires revision on the basis of the evidence herein presented. Mucus production is the function of the columnar cells, which cover the surface and line the glands. The amount of mucus produced will depend on the number and intrinsic functional ability of these cells. Both these functions in the cervical mucosa, the proliferation and secretion of the columnar cells, are under hormonal influence. It has been proved by several investigators (Burch,⁸ Parkes,⁹ Tietze,¹⁰ Kaufman¹¹) that estrogen is responsible for the proliferation of the columnar cells in the endometrium. I had the opportunity to experiment on a castrated woman and was able to change an atrophic endocervix into one of the late proliferative type by the administration of large doses of estrin. A detailed report of my observations in this case will be published at some future time. Estrogen increases the size and number of glands in the cervical mucosa as it does in the endometrium. While it is impossible to give exact statistical figures, the study of a large number of specimens of cervical mucosa in the different phases of the intermenstrual period makes it evident that a progressive development of the glandular element takes place in the endocervix. Under normal hormonal activity the absolute number of glands is small in the earliest proliferative phase, and this is followed by a gradual increase in number and size until the peak of estrin production is reached. The increased cervical discharge preceding menstruation, which is a common clinical observation, is physiologic and a concomitant of the ovarian hormone influence on the cervical mucosa.

Glandular hyperplasia with subsequent hypersecretion may be a hormonal phenomenon in the light of our newer knowledge of endocrine function. Our conception of the normal ovarian cycle is a developing and ripening follicle with increasing estrogenic activity followed by ovulation, when the activity of the corpus luteum hormone begins. As the progestin's activity increases, there is a decrease of estrogen activity, and it is believed that the progestin elaborated is able to counteract the effects of estrogen activity. Macroscopic inspection of ovaries in the course of laparotomies, performed on normally menstruating women, indicates that the ovarian mechanism cannot be placed on such a simple

basis. On the surface of even normal ovaries a number of unruptured follicles can often be seen. In one case I withdrew into small syringes the fluids contained in small follicles and had them assayed, with the result that in each of the follicles active estrogenic substance could be detected. Although it seems that in mild cases small follicular cystic areas do not disturb normal menstruation, doubtlessly the cumulative effect of estrogen contained in supernumerous follicles alters the normal hormonal balance in the ovaries and must be reflected in the histologic picture of the mucous membranes. In my cervical specimens I noted a great variation in the absolute number of glands and found them always proportionate to the number of glands in the endometrium. Since we know that estrogenic production regulates the number of glands, a hypersecretion of this hormone is bound to manifest itself by an increased amount of mucus from the cervical canal.

On the basis of my observations it seems likely that in the terminology of endocervicitis we are confronted with problems similar to those pertaining to endometritis after Hitschman and Adler's classic researches. Before the recognition of definite endometrial cyclic changes, certain physiologic transformations of the endometrium were erroneously diagnosed as endometritis. Glandular hyperplasia, which we now know is the result of hormonal hyperfunction, was diagnosed as inflammatory condition.

My research work on the cervical mucosa up to the present time justifies the conclusion that in the study of endocervicitis hormonal factors have to be taken into consideration, and further investigations promise a more scientific understanding of this gynecological problem. The more our research work on the histologic features of the menstrual cycle broadens, the more apparent it is that at present we possess only a meager knowledge of this intricate process. Much more labor in this field is necessary to explain the details of the sexual mechanism. A prerequisite for continued progress in gynecologic endocrinology is an exact knowledge of the sex cycle in normal human beings. It is to be hoped that the utilization of the periodic cervical biopsy method, which I strongly advocate for the study of normal women will be instrumental in developing a better knowledge of the action of the female sex hormones.

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THE CAUSES OF VAGINAL BLEEDING AND THE HISTOLOGY OF THE ENDOMETRIUM AFTER THE MENOPAUSE

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ABNORMAL gynecologic bleeding has a wide variety of causes which differ in their relative importance depending upon the age groups being studied. The change in the causes of this symptom which occurs at the menopause overshadows, however, the change taking place between any two decades. On account of its peculiar significance therefore, bleeding after the menopause is correctly regarded as a special entity by both clinician and pathologist. The chief clinical importance remains the significance of the symptom in the diagnosis of cancer, while pathologic attention is directed at present to the study of late functional reactions in the endometrium and their relationships to neoplastic or other changes in the ovary.

I. GENERAL EFFECT OF INCREASING AGE AND THE MENOPAUSE ON THE CAUSES OF ABNORMAL GYNECOLOGIC BLEEDING

During the fifteen-year period from 1921 to 1935 there were admitted to the Gynecologic Service of the Roosevelt Hospital 12,350 patients of whom 4,362 noted some form of abnormal vaginal bleeding, menorrhagia, metrorrhagia, or a sanguineous discharge. In this study of the causes of vaginal bleeding these cases have been classed according to their diagnosis on discharge from the hospital. When two or more possible causes of bleeding were indicated by this diagnosis, the more probable was accepted according to an occasionally arbitrary but always uniform plan.

The cases were subdivided first according to physiologic age, and second according to decades. Accordingly the decades of 40 to 49 and 50 to 59 each appear twice in Chart 1, a patient being placed in one or the other, depending upon whether she had or had not experienced her menopause. The criterion for regarding a patient as having had her menopause was at least six months of amenorrhea occurring after the age of 40 and preceding the bleeding for which she was treated.

From this preliminary classification (Chart 1), a few points may be emphasized.

✓ 1. The relative frequency of functional and unexplained causes of bleeding remains about the same in any decade before the menopause, but decreases thereafter. The peak in total incidence is in the thirties.

2. Bleeding due to some complication of pregnancy, particularly abortion or ectopic pregnancy, has of course its principal incidence in the twenties with a high relative incidence even before that time.

3. Inflammatory disease, usually an endometritis associated with adnexal inflammation, has a similar incidence to that of the complications of pregnancy. Inflammation as an important cause of sanguineous vaginal discharge, however, persists in the form of cervical erosions or senile vaginitis in the menopause.

4. Benign tumors show both their greatest absolute and relative frequency as causes of bleeding shortly before the menopause, due of course to the well-known age incidence of fibroids. There is an abrupt drop in the relative frequency of these tumors after the physiologic change of the menopause.

5. The relation of the menopause to the probability of cancer as the cause of bleeding is spectacularly shown in this chart. The rise in the actual number of cancer cases is less abrupt, beginning in the thirties with cases of cancer of the cervix and maintained after the menopause by the increased frequency of cancer of the corpus.

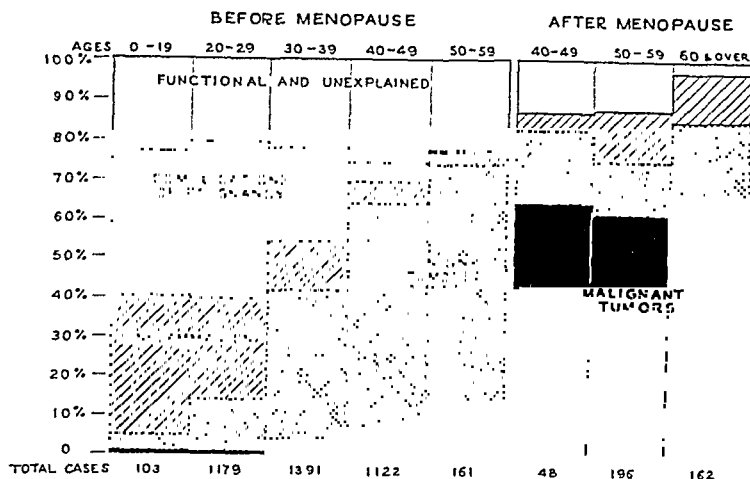


Chart 1.—Relative frequency of causes of gynecologic bleeding in 4,362 cases.

The physiologic change of the menopause is thus far more important in determining the probable cause of bleeding than is any change of a decade in actual years. A woman who is still menstruating, but bleeding abnormally in her fifties, is much less likely to have cancer than is a patient in her forties who experiences a return of bleeding after an early menopause.

II. THE CAUSES OF POSTMENOPAUSAL BLEEDING

The causes of bleeding in the menopause have been classed under four main heads, malignant tumors, inflammation, benign tumors, and functional or unexplained bleeding.

A. *Malignant Disease in the Pelvis.*—Of the 406 patients with postmenopausal bleeding in this series, 259 (63.3 per cent) were associated with some form of cancer. The distribution of these cases is seen in Table I.

Many series of figures have shown that cancer is present in about two-thirds of the patients admitted to hospital services with postmenopausal bleeding. The following figures may be cited: Kantner and Klawans, 68.4 per cent; Fahmy, 43.12 per cent; Geist and Matus, 57.5 per cent; Norris, 52.9 per cent; Zweifel, 87 per cent; Benthin, 42.7 per cent; Brown, 66.8 per cent; Motta, 74.6 per cent; Pemberton and Lockwood, 50.8 per cent; Keene, 61.4 per cent; Ducuing, 92 per cent.

TABLE I. MALIGNANT TUMORS IN CASES OF POSTMENOPAUSAL BLEEDING

	AGES 40-49	AGES 50-59	AGES 60-80	TOTAL
Carcinoma of cervix	22	54	49	125
Carcinoma of corpus	3	53	45	101
Carcinoma of vagina	1	2	6	9
Carcinoma of vulva	3	2	2	7
Carcinoma of ovaries	0	6	2	8
Granulosa cell tumors	0	4	0	4
Myosarcoma of uterus	2	0	3	5
Total	31	121	107	259

These cited statistics are based on hospital patients in whom the incidence of major lesions is of course high. A study of a group of 291 patients with similar symptoms but seen in office practice gave an incidence of malignant disease of only 38.1 per cent (Table II). Even in

TABLE II. PROPORTION OF MALIGNANT CASES IN OFFICE PATIENTS WITH POSTMENOPAUSAL BLEEDING

	NUMBER	PER CENT
Malignant tumors	111	38.1
Benign lesions	180	61.9

the private practice of a gynecologist, however, there is an unusual number of referred cancer cases to continue the emphasis upon cancer as a cause of postmenopausal bleeding. It is probable that of the cases of postmenopausal bleeding which come originally to the family physician as an unsorted group that no more than a fifth have a malignant tumor. This figure is enough to demand care in treatment, but not enough to cause the despair with which the symptom is often greeted.

B. *Benign Inflammatory Lesions.*—This group consists for the most part of the visible inflammatory lesions of the vagina and cervix. Of this group there are 46 cases (Table III).

TABLE III. POSTMENOPAUSAL BLEEDING FROM INFLAMMATORY LESIONS

	AGES 40-49	AGES 50-59	AGES 60-80	TOTAL
Senile vaginitis	0	6	5	11
Prolapse of uterus. Erosion of cervix	0	7	8	15
Erosion of cervix	2	11	5	18
Acute salpingitis	0	0	2	2
Total	2	24	20	46

1. *Senile vaginitis* was the apparent cause of bleeding in 11 patients who were nearly all admitted to the hospital because of doubt as to the diagnosis. This lesion would, of course, be much more common in a group of patients selected from the clinic or office. In two cases of this series, the vaginitis was due to a pessary kept in the vagina over a long period and removable only under anesthesia.

2. *Prolapse of the uterus with erosion of the cervix* was the basis of symptoms in 15 patients all of whom complained of bloody discharge but were operated upon chiefly for the malposition of the uterus. No

lesion of the endometrium was found otherwise to explain the bleeding in 9 of the 10 cases curetted in this group. In one there were signs of a mild endometritis.

3. *Erosion of the cervix*, unsubjected to the trauma that occurs with prolapse, is a more doubtful lesion with which to explain bleeding. Nevertheless in the 15 cases in which a curettage was performed a possible alternative explanation was found in only two.

4. *Salpingitis*: In 2 patients the bleeding was associated with acute inflammatory disease in the pelvis. In neither of these cases was the endometrium available for examination.

5. *Chronic endometritis* has not been classed with the inflammatory lesions because of its doubtful status as a cause of bleeding. It is probably a precipitating cause of the bleeding in cases of submucous fibroids, and possibly in association with erosion and endocervicitis in elderly women. It may exist as a relatively independent lesion as will be discussed below.

C. *Benign Tumors*.—Bleeding occurred in 67 patients in whom benign tumors were present (Table IV). These played a variable role in the production of the symptoms.

TABLE IV. POSTMENOPAUSAL BLEEDING WITH BENIGN TUMORS

	AGES 40-49	AGES 50-59	AGES 60-80	TOTAL
Fibromyomas	7	8	13	28
Fibromyomas and ovarian tumors	1	4	3	8
Ovarian tumors only	0	2	1	3
Cervical polyps	0	9	6	15
Endometrial polyps	1	3	5	9
Urethral caruncles	0	1	3	4
Total	9	27	31	67

1. *Cervical polyps* apparently alone accounted for the bleeding in 15 cases, and 2 more associated with fibroids were possible causes. No doubt many more were treated in the dispensary and offices of the physicians referring patients to the indoor service.

2. *An endometrial polyp* as an uncomplicated lesion was an acceptable cause of bleeding in only nine cases, but such a polyp was found in association with fibroids in five more. This is a relatively low figure, for Benthin found that these growths were responsible for about a quarter of all of his cases of benign postmenopausal bleeding from the body of the uterus.

3. *Fibroids of the uterus* were the most frequent benign tumors noted in this series, a finding contrary to a belief widely held that these tumors cease to cause trouble after the cessation of the menses. The contradiction is only apparent, however, because, as is shown in Table V the bleeding was due in a great majority of the cases not to the tumor itself, but to some special complication. Other investigators such as Shaw have emphasized degeneration of the fibroid as the chief cause of trouble in the menopause, but in this series it is clearly the necrotic and inflammatory changes developing in the submucous pedunculated

TABLE V. COMPLICATIONS AS A FACTOR IN BLEEDING FROM A UTERUS WITH FIBROIDS AFTER THE MENOPAUSE

	TOTAL CASES
Submucous position	12
Ovarian tumors	8
Endometrial polyps	5
Cervical polyps	2
Endometrial hyperplasia	2
Late menstruation	3
Prolapse of uterus	4
(Carcinoma of corpus)	(44)
Total	80

tumor which are chiefly responsible for the bleeding. This list of 36 patients with fibroids includes only benign cases, but in 44 more fibroids were associated with cancer of the body of the uterus. Therefore if all cases of bleeding from the body of the uterus in which fibroids were present are considered, it is found that carcinoma is present in more than half.

4. *Benign ovarian tumors* were the only gross lesions present in three cases, but in eight others, there was bleeding from a fibroid in the uterus,

TABLE VI. POSTMENOPAUSAL BLEEDING WITH OVARIAN TUMORS

	PATH. NO.	AGE	ENDOMETRIUM	OVARY
<i>Group 1. Bleeding With Benign Ovarian Tumors. Normal Myometrium</i>				
1	S.C. 3871	53	Normal	Pseudomucinous cystadenoma
2	S.C. 3029	52	Atrophic	Papillary serous cystadenoma
3	S.A. 9449	61	No specimen	Pseudomucinous cystadenoma
<i>Group 2. Bleeding With Benign Ovarian Tumors. Fibromyoma Uteri</i>				
4	S.B. 7019	75	Hyperplasia	Pseudomucinous cystadenoma
5	S.C. 1283	59	Atrophic, cystic	Pseudomucinous cystadenoma
6	S.B. 2593	54	Atrophic	Pseudomucinous cystadenoma
7	S.B. 5109	60	Atrophic, adenomyosis	Pseudomucinous cystadenoma
8	S.C. 199	50	Atrophic, polyp	Papillary serous cystadenoma
9	S.C. 1872	61	Atrophic, polyp	Serous cyst
10	S.C. 4312	48	Atrophic	Serous cyst
11	S.B. 2973	58	No specimen	Parovarian cyst
<i>Group 3. Bleeding With Granulosa Cell Tumors</i>				
12	S.B. 6383	58	Hyperplasia	Sarcomatous type
13	S.C. 1457	55	Hyperplasia	Diffuse type with luteinization
14	S.C. 9046	59	Hyperplasia	Theca cell type
15	S.C. 1412	52	Hyperplasia	Cylindromatous type
	S.C. 6240			
<i>Group 4. Bleeding With Malignant Ovarian Tumors</i>				
16	S.B. 5648	58	Adenocarcinoma	Papillary cystadenocarcinoma
17	S.B. 8060	58	Adenocarcinoma	Papillary cystadenocarcinoma
18	S.C. 5032	60	Adenocarcinoma	Papillary cystadenocarcinoma
19	S.C. 5577	74	Adenocarcinoma	Papillary cystadenocarcinoma
20	S.C. 5782	55	Hyperplasia	Papillary pseudomucinous cystadenocarcinoma
21	S.C. 6569	55	Adenocarcinoma	Papillary cystadenocarcinoma
22	S.D. 2793	52	Atrophy, polyp	Papillary pseudomucinous cystadenocarcinoma
23	S.C. 1130	52	Atrophy	Papillary cystadenocarcinoma

with a benign ovarian tumor also present. To complete the group of cases of bleeding with ovarian new growths there must be also added 8 cases of typical ovarian adenocarcinoma, and four cases of tumors of the granulosa cell type.

The subject of postmenopausal bleeding with ovarian neoplasms has recently received much attention on account of the indication that it gives of a hormone activity of the tumor. Too little emphasis has perhaps been given to the fact that bleeding in the presence of an ovarian tumor is not necessarily a sign that a specific tumor, such as the granulosa cell tumor, is the cause.

Table VI shows that bleeding in association with ovarian tumors may occur under several circumstances.

a. *With an associated carcinoma of the endometrium*, a coincidence occurring in five instances in this series. Whether the tumor is primary in the fundus or in the ovary or whether the tumors are independent coincident growths cannot always be determined.

b. *With an associated hyperplasia of the endometrium*. The relationship of the endometrial lesion to the ovarian tumor is established to a variable degree for the different forms of ovarian neoplasm.

1. The typical granulosa cell tumor is an accepted cause of hyperplasia of the endometrium in the menopause. There were two tumors of this class in the series, one a typical cylindromatous form, the other with signs of luteinization of the granulosa cells.

2. A group of tumors whose structure resembles more closely the stroma of the ovary has a debatable relation to the granulosa cell tumors. Meyer in 1925 reported endometrial hyperplasia in two cases of sarcoma and in one of fibroma of the ovary, but suggested that these might be derived from granulosa cell tumors. More recently there has been an attempt to segregate a new group of tumors, having hormone activity, as theca cell tumors (Loeffler and Priesel, Melnick and Kanter, Geist and Spielman). Novak and Brawner prefer to regard all these tumors as part of the granulosa cell group and as justification cite the theory of a common origin of granulosal, thecal, and stromal tissue from the ovarian mesenchyme (Fischel). According to the conception that one holds, the two tumors of this group may be regarded as granulosa cell tumors, or Case 12 may be considered a sarcoma and Case 14 a fibroma or theca cell tumor.

3. Nonspecific ovarian tumors have occasionally been reported in association with endometrial hyperplasia, but their position as hormone producers has not been accepted. In two patients, one with a pseudomucinous cystadenoma and one with a pseudomucinous cystadenocarcinoma, the endometrium showed numerous glands with a high cylindrical epithelium and large cystic glands. In a third endometrium, also associated with a pseudomucinous cystadenoma, although hyperplasia could not be said to be present, the expected degree of atrophy had not occurred.

CASE 1.—R. N. (History 14659), a 75-year-old married woman, para iv, was admitted for two weeks of vaginal bleeding after not having menstruated for twenty-five years. At operation (Aug. 13, 1926) there were found a cyst, 23 cm. in diameter, of the left ovary, several small fibroids of the uterus, and a nodular area in the right breast. Pathologic examination (S.B. 7019) led to a diagnosis of pseudomucinous cystadenoma of the left ovary, atrophy of the right ovary, fibromyomas of the uterus, chronic cystic mastitis, and hypertrophy of the endometrium. Sections of the endometrium showed many dilated glands of variable size with a well-preserved cuboidal epithelium (Fig. 1).

CASE 2.—(History 19326.) A married woman of 55 years, with two children, was admitted with a history of two recent attacks of vaginal bleeding, beginning fifteen years after her menopause. At operation (Aug. 19, 1931) a 25-cm. cyst of the left

ovary, containing a clear straw-colored fluid, was found and removed. Within the wall was a localized, projecting solid area of evident malignancy. The complete operation consisted in a supravaginal hysterectomy, bilateral salpingo-oophorectomy, and insertion of radium (1800 mg. hours) into the cervical stump. The pathologic report (S.C. 5577) included pseudomucinous cystadenocarcinoma of the left ovary; fibrosis of the right ovary; hyperplasia of the endometrium. Sections of endometri-

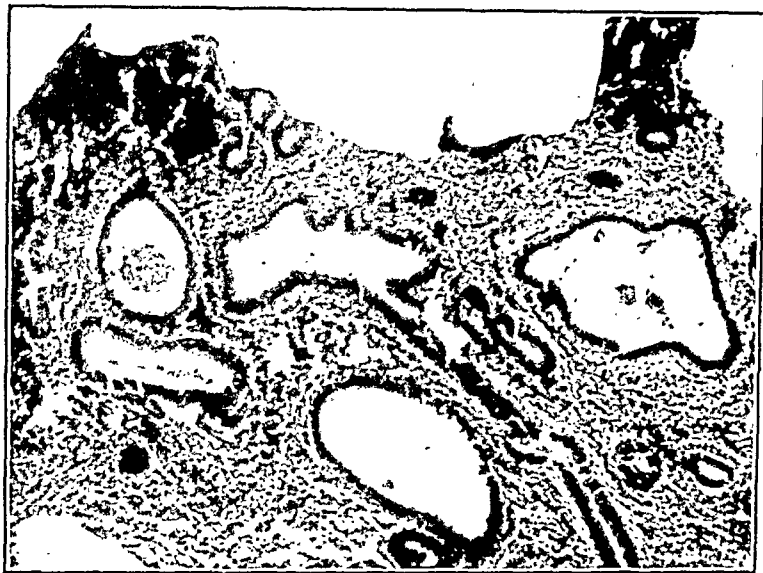


Fig. 1.—Cystic hyperplastic glands in a patient of 75 years, with a pseudomucinous cystadenoma (S.B. 7019).

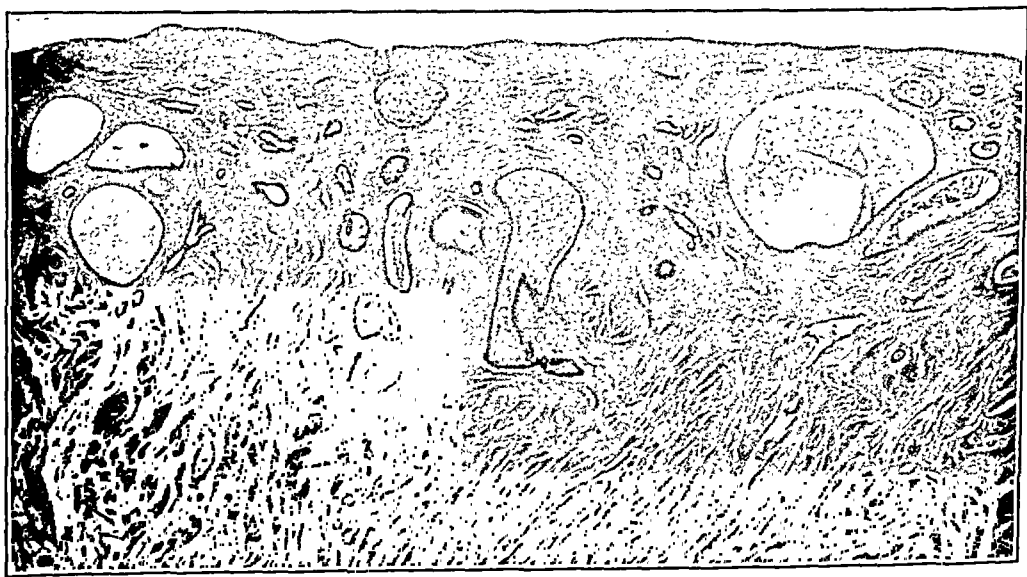


Fig. 2.—Cystic and hyperplastic glands in a patient of 55 years with pseudomucinous cystadenocarcinoma (S.C. 5577).

um (Fig. 2) showed a mucosa of medium thickness, overlying muscle with numerous slender glands and among these, but especially in the basal portions of the endometrium, large dilated cystic structures.

Moulouguet and Doléris, Tietze, and Schiffmann have likewise noted moderate degrees of hyperplasia of the endometrium with several nonspecific types of ovarian tumor. The case which Tietze took for illustration was a mucus-producing adenocarcinoma similar to cases of the present report. Schiffmann has described hyper-

plasia with a Brenner tumor and a pseudomucinous cyst in a woman of 60 years, and an endometrium manifesting at least no evidence of atrophy in a patient of 74 years with a bilateral mucus gland carcinoma of the ovaries.

According to Schiffmann's view, one cannot exclude the possibility of an ovarian effect from these growths, although the hyperplasia is less marked than in the granulosa cell tumors. Tietze, however, expressed the belief that this hyperplasia with the nonspecific ovarian tumors was not an abnormal functional phase but the result of local increased metabolism and blood supply. Whatever may be the cause of the hyperplasia in these cases, the microscopic picture is sufficiently like that produced by the granulosa cell tumors to make it inadvisable to draw ready conclusions as to the character of any palpable ovarian tumor when such endometrial tissue is obtained at curettage.

c. *In the presence of an atrophic endometrium.* In 7 patients bleeding occurred in the presence of an ovarian tumor from an atrophic endometrium. To explain such bleeding it has been customary to assume a pelvic congestion as a result of the tumor with bleeding from the engorged veins in the endometrium. Such distended vessels in the endometrium were evident in several of our specimens. Unrelated causes such as endometritis may be a factor.

D. *Bleeding From Grossly Normal Uteri.*—There remains finally a group of 34 patients in whom no gross inflammatory or neoplastic lesions were demonstrable anywhere in the pelvis (Table VII). For these an essentially endometrial source for the bleeding must be sought.

TABLE VII. BLEEDING FROM GROSSLY NORMAL UTERI

	AGES 40-49	AGES 50-59	AGES 60-80	TOTAL
Prolapse of uterus. Congestion(?)	1	7	1	9
Functional bleeding:				
Interval phase	3	4	0	7
Premenstrual phase	0	1	0	1
Hyperplasia	0	1	2	3
Endometritis in atrophic endometrium	1	6	0	7
No assignable cause:				
Simple atrophy	1	4	1	6
No endometrium	0	1	0	1
Total	6	24	4	34

1. *Vascular Lesions:* The view has been repeatedly expressed that hypertension or chronic passive congestion from a failing heart might be associated with uterine bleeding (Rees, Klotz and Klotz), but instances of systemic cardiac or vascular disease did not occur with unusual frequency in this series of cases. Localized lesions of blood vessels are a more probable source of bleeding. Lahm has emphasized disturbances in circulation but noted also local trauma and constipation as precipitating causes. In nine of the cases of this group, various degrees of uterine prolapse were present as a theoretical source of the venous congestion which might lead to this uterine bleeding.

2. *Endometritis* has been suggested as a cause of postmenopausal bleeding, the inflammation being laid sometimes to cervical stenosis with interruption of proper drainage, sometimes to the loss after the menopause of the protecting plug of cervical mucus. Benthin places inflammations of the endometrium at the head of his list of the benign causes of uterine bleeding in the menopause, and other writers (Breipohl) have given it a prominent position.

The importance of inflammation is difficult to evaluate on the minute fragments of tissue obtained from the senile uterus by curettage. The appearance of many inflammatory cells in tiny fragments of uterine tissue does not determine that the inflammation was the exciting cause of the bleeding, and the reverse may actually

be the case. Histologic evidence of an inflammatory reaction of some sort was present in seven of the 26 cases in which the uterus was grossly normal. Histologic evidence of this endometritis is most definite, however, in fragments of tissue obtained from uteri in which fibroids or polyp are present (Fig. 3).

3. *Late Ovarian Activity*: The possibility of renewed function of the ovary after months or years of apparent inactivity has received little attention until recently. That the endometrium after castration (Kaufmann) or even in extreme old age (Hübscher) could be stimulated to renewed activity by administration of an estrogenic hormone has been proved, and bleeding has been produced artificially. Attempts to reactivate the human ovary, however, have led to contradictory results. Tschertok and Penkow failed to obtain any reaction in ovaries of women injected with pregnancy urine before celiotomy for fibroids, but Westman, who performed similar experiments, claimed to have observed follicle growth and corpus luteum formation.



Fig. 3.—Chronic endometritis in a patient of 64 years with an endometrial polyp (S.B. 8949).

In reply to this work of Westman, Waldeyer has recently reported in a series of untreated patients, forty-eight to fifty-four years of age with their menopause from three months to five years behind them, follicle and early corpus luteum development in the ovary and an interval phase of the endometrium. Breipohl in studying the endometria of 130 women over forty-five years of age and at least six months after their supposed menopause, reported 13 with endometria in the proliferative stage and three in a secretory stage. Robert Meyer has also reported a corpus luteum in the menopause.

a. *Interval endometrium*: In the present series, among the 35 cases with normal pelvic organs there were seven (ages 47, 49, 47, 55, 52, 55, 52) in which little or no atrophy could be noted. Their histology resembled in some respects the interval phase of the normal endometrium, but the glands were less regular and often cystic, and the stroma somewhat dense. In several it was difficult to decide whether to list them as cases of hyperplasia, of which the following case report is an example.

CASE 3.—F. S. (History 14396.) This married childless woman, 55 years of age, was admitted with a history of "metrorrhagia." The uterus was noted as in mid-

position and a little "heavy," the right adnexa prolapsed, the cervix normal. The operation (May 12, 1926), consisting in a dilatation, curettage, and insertion of radium, led to a pathologic diagnosis of hyperplastic endometrium (S.B. 6563). Review of this material showed a surface epithelium of high columnar cells, many round well-formed glands (Fig. 4) whose cells in places showed slight evidence of secretion and finally a few cystic glands, irregular in shape, but still with a well-developed epithelium.

b. Premenstrual endometrium: An early premenstrual phase was found in a patient of 55 years in the group with normal pelvic organs and a fully developed secretory endometrium in a patient of 52 years with a fibroid uterus.

CASE 4.—G. M. (History 18783.) This patient, a 55-year-old married woman with two children was admitted on account of five days of profuse vaginal bleeding after a year's freedom from any regular menstruation. Very slight bleeding had occurred, however, at frequent, perhaps approximately monthly, intervals. The op-



Fig. 4.—Absence of atrophy in endometrial glands of a patient of 55 years (S.B. 6563).

eration (Jan. 28, 1931) consisted in a plastic operation on the vaginal walls and cervix and a curettage with insertion of radium. The pathologic report (S.C. 4581) was "moderate hypertrophy of the endometrium," but re-examination showed in places the rows of irregular gland sections, indicating the tortuous glands of the early premenstrual phase (Fig. 5).

CASE 5.—F. B., History 13503. This 52-year-old patient, the mother of 4 children, had had an apparent menopause at 50, but after skipping several months had, nine months before her admission, begun to bleed at irregular intervals. Examination showed the fundus to be somewhat enlarged and irregular, the cervix and adnexa normal. The operation consisted in a plastic operation on the vaginal walls, a dilatation and curettage and insertion of radium. The pathologic report of the tissue (S.B. 4641) was hyperplasia of the endometrium. Review of the slides has shown a typical premenstrual endometrium with tortuous glands, cells filled with secretion, edema and inflammatory cells in the stroma (Fig. 6).

CASE 6.—In a recent case not belonging to the present series but operated upon at the Bellevue Hospital, a fully developed premenstrual endometrium was encountered in a patient of 55 years. This woman had had bleeding at intervals of several months for two or three years without the establishment of a definite menopause.

Abdominal operation was undertaken because of urinary symptoms and a cystoscopic report of a tumor pressing on the bladder. The uterus was found to be symmetrically enlarged, soft, discolored and a complete hysterectomy with removal of both adnexa was undertaken because of the belief that a carcinoma of the corpus was present. Sections revealed a typical premenstrual endometrium and a corpus luteum in one ovary.



Fig. 5.—Early premenstrual endometrium in a patient of 55 years (S.C. 4581).



Fig. 6.—Typical premenstrual endometrium in a patient of 52 years (S.B. 4641).

These three cases indicate that up to the age of 55 years and even after intervals of amenorrhea of several months, a normal menstrual period may be the explanation of vaginal bleeding. In none of the cases studied, however, has a typical premenstrual endometrium been found in a woman who, having passed the age of 50, had had more than twelve months of amenorrhea.

c. Hyperplasia of the endometrium. Although endometrial hyperplasia has been regarded as rare after the menopause, cases were reported some time ago by Seitz and by Meyer. In Meyer's case, a woman of 61 years, the failure of three curettages and the success of radiation of the ovaries led to the suggestion that even at this age the ovaries might have an endocrine effect. Endometrial hyperplasia was reported by one of the writers (Taylor) as frequently present near areas of carcinoma of the endometrium, a finding corroborated and amplified by Novak and Yui. Breipohl in a survey of the endometria of the menopause found 15 or 11.53 per cent to be hyperplastic.

Among the 34 patients with otherwise normal pelvic organs in the present series, endometrial hyperplasia was found in three, aged 53, 63, and 63 years, who had had their menopause 13, 13, and 4 years, respectively, before their operation. Among the patients with fibroids uncomplicated by ovarian tumors, there were also 2 cases of hyperplasia, but each of these occurred relatively soon after the menopause. The frequency with which hyperplasia was encountered among these cases of post-menopausal bleeding appears thus to be considerably less than that observed by

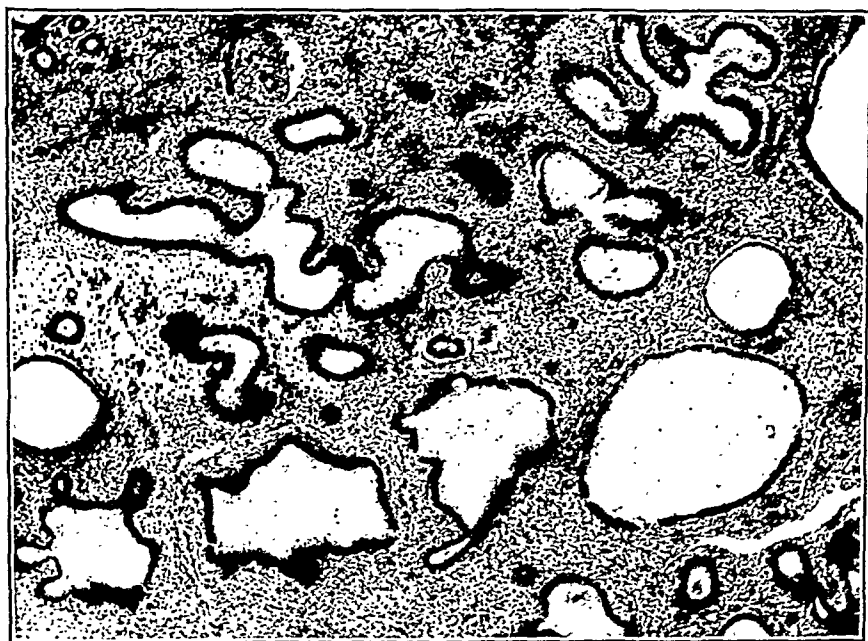


Fig. 7.—Endometrial hyperplasia in a patient of 63 years, ten years after the menopause (S.B. 6979).

Novak and Yui or by Breipohl, but since the cases were selected for different reasons, the material is not wholly comparable. The histories of the three older patients are as follows:

CASE 7.—E. A. (History 14613.) This married woman of 63 years, the mother of 7 children, had had a normal menopause at the age of 53, had bled for six days with clots at the age of 61, and now again for six days before admission. Physical examination disclosed no abnormalities. The operation consisted in a curettage and insertion of radium. The endometrium, which could be curetted away in fairly large fragments, was diagnosed as "hyperplastic endometrium" (S.B. 6979). The sections (Fig. 7) of this tissue showed irregular branching as well as cystic glands in a rather dense stroma.

CASE 8.—J. H. (History 15403.) This patient, a married woman of 63 years with 2 children, stated that her menopause had not occurred until her fifty-ninth year after which there had been no bleeding until a slight show of blood two weeks before admission. Examination disclosed a somewhat enlarged uterus and otherwise normal pelvic organs. The operation (June 13, 1927) consisted in a dilatation and curettage and the insertion of radium. The pathologic report (S.B. 8566) was

hypertrophy of the endometrium. Review of the sections (Fig. 8) showed a tissue containing many cystic glands of irregular contour and many smaller glands occurring packed together in clusters. The cells of the epithelium were small, cylindrical with the nuclei practically filling the cells. The stroma was dense, cellular infiltrated with blood.

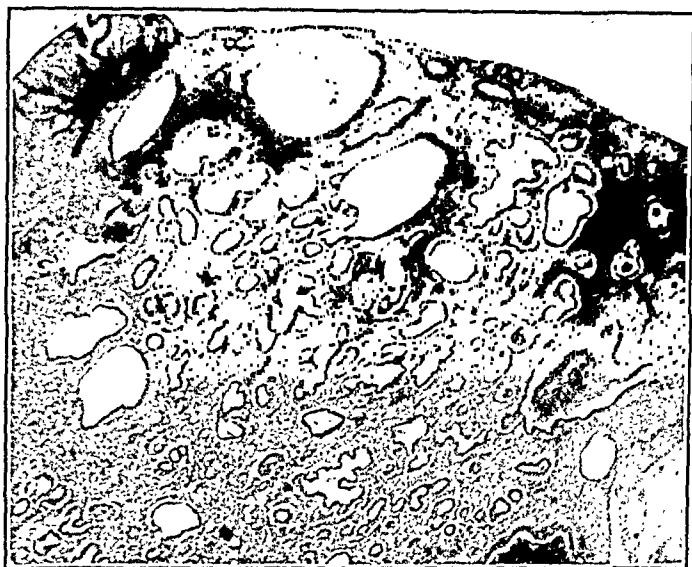


Fig. 8.—Endometrial hyperplasia in a patient of 63 years, four years after the menopause (S.B. 8566).



Fig. 9.—Endometrial hyperplasia in a patient of 58 years, thirteen years after her menopause (S.B. 3025).

CASE 9.—N. O. (History 12650.) This married woman of 58 years, the mother of 9 children, had had a normal menopause at 45, but had again been bleeding slightly for three months before admission. Examination showed the fundus, cervix, and adnexa to be grossly normal. The operation consisted in a curettage and insertion of radium. The pathologic report (S.B. 3025) was chronic endometritis. Review of the sections (Fig. 9) showed numerous glands, mostly quite round but of all sizes. The epithelium in the different glands was strikingly variable, being very

low in some, high columnar in others. The stroma again was cellular, but very dense. This patient continued to bleed and was curetted again on April 25, 1935, but at that time only degenerated tissue was obtained by curettage. No ovarian tumors were ever palpable.

The hyperplasia developing after the menopause is thus in some respects histologically different from that appearing earlier. The stroma tends to be cellular but rather dense. The glands are very irregular in shape, frequently branching, often flattened, and sometimes showing small intraglandular papillae. Occasionally, however, the glands are round and cystlike with a flattened cellular lining. The epithelium of adjacent glands is often strikingly dissimilar, all variations being present from flat to high columnar cells. The process suggests a renewed growth of some glands superimposed upon an atrophy of the old mucosa.

The basis of the late hyperplasia is open to considerable dispute. Two principal views are admissible. First the cause of the hyperplasia may be the ovarian hormone, as is true for the younger cases, but special consideration is necessary to explain its source. It is possible first that small granulosa cell tumors may be present and yet not evident to the examiner. This occurrence has been previously reported,

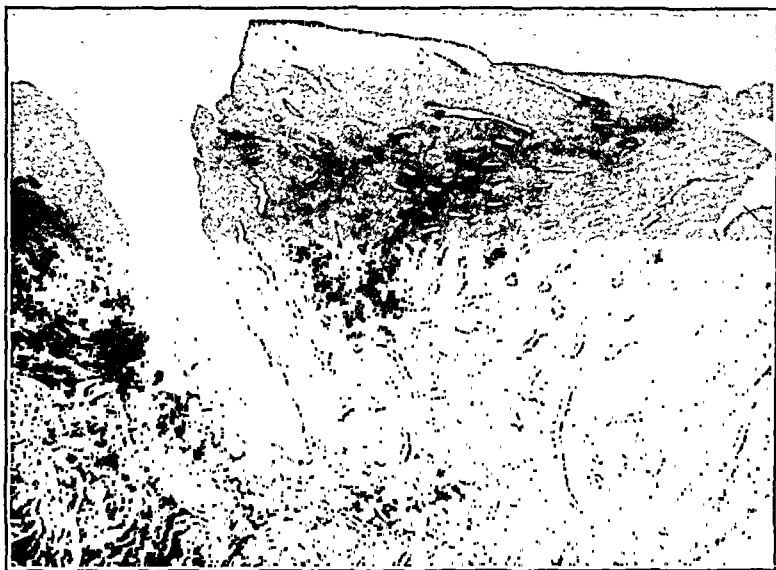


Fig. 10.—Localized hyperplasia or polyp of endometrium (S.D. 2793).

and one of our own cases of granulosa cell tumor was missed at the time of the patient's first curettage for postmenopausal bleeding. Second, a late development of follicles may be responsible, for cystic conditions of the ovary have in fact been reported many years after the menopause. Whether these form the estrogenic hormone in amounts sufficient to influence the endometrium is not known. Considerable quantities of estrogenic hormone do continue to be excreted in the urine many years after the menopause and even in castrates (Frank, Goldberger and Salmon). The latter indicates an extraovarian source for this substance which again may be a basis for endometrial proliferation. It is finally a possibility that the histologic change produced by the ovarian function at or before the menopause may persist for years to give the impression of a late ovarian activity.

The second major conception is that this hyperplasia is a process of a less physiologic and more neoplastic character due to other types of stimuli, perhaps purely local. In material obtained by curettage it is in fact often difficult to determine whether one is dealing with fragments of small polyps or a strip of endometrium. But besides the confusion due to technical deficiencies there are probably more or less transitional forms between purely localized polyps and diffuse hyperplasia. Fig. 10 shows a flat, plateau-like structure arising a little above the remaining endometrium, which is apparently a localized process but which has a wide

TABLE VIII. THE ENDOMETRIAL FINDINGS IN THE MENOPAUSE*

CLASSIFICATION OF CAUSE OF BLEEDING	AGE 40-49						AGES 50-59						AGES 60-80									
	ATROPHY	INTERVAL PHASE	PREMENSTRUAL PHASE	HYPERTPLASIA	ENDOMETRIAL POLYP	CARCINOMA	NO ENDOMETRIUM	ATROPHY	INTERVAL PHASE	PREMENSTRUAL PHASE	HYPERTPLASIA	ENDOMETRIAL POLYP	CARCINOMA	NO ENDOMETRIUM	ATROPHY	INTERVAL PHASE	PREMENSTRUAL PHASE	HYPERTPLASIA	ENDOMETRIAL POLYP	CARCINOMA	NO ENDOMETRIUM	
Senile vaginitis	11	0					0	5						1	3							3
Prolapse. Cervical erosion	15	0					0	5						1	3							3
Cervical erosion	18	1	1					9						3	5							3
Salpingitis	2						2	4		1		(2)		3	6				(1)			7
Uterine fibroids	28	1	2	2				3				(1)		1	2			1	(1)			1
Fibroids and ovarian tumors	8	1						1	1					1	3							1
Benign ovarian tumors	3							3						6	2							6
Cervical polyps	15						1	3				(3)		3	2				(5)			5
Endometrial polyps	9							2						1	2					(2)		2
Urethral caruncles	4							2				(1)	(3)	3								1
Carcinoma of ovary	8							2						1	2							1
Granulosa cell tumors	4							2						4	1							1
Simple prolapse of uterus	9						1	10	4	1	1			4	1			2				1
Normal pelvic organs	25	2	3					10	5	2	6			1	1							25
Total	159	5	6	2	(1)		4	45	5	2	6	(7)	(3)	27	25			3	(7)	(2)		29

*NOTE: Endometrial polyps and carcinoma are included in parentheses since they represent local conditions and not the character of the endometrium itself.

*NOTE: Endometrial polyps and carcinoma are included in parentheses since they represent local conditions and not the character of the endometrium itself.

base and none of the gross anatomic characteristics of a polyp with a pedicle. There is no reason to suppose that all types of endometrial gland hyperplasia are directly or immediately caused by the estrogenic hormone, and there is much to favor an opposite viewpoint.

SUMMARY OF ENDOMETRIAL FINDINGS

The endometrium of the cases of cancer of the cervix, vulva or vagina were available in a few cases only, and that associated with carcinoma of the corpus had been previously reported upon (Taylor). Endometrial specimens were available in 99 of the remaining cases.

Atrophy was the condition present in 75, or approximately three-fourths of the cases. This was the finding in 4 of 13 patients under 50 years, in 45 of 58 patients between 50 and 59, and in 25 of 28 patients after 60.

A nonatrophic endometrium was present 11 times, or in 6 of 13 patients under 50 and in 5 of 58 patients between 50 and 59 years. It was never observed after 60 years of age. This indicates that some years are required in many cases before atrophy recognizable in curetted material develops, or possibly that recrudescences of minor ovarian activity may occur. Its absence after 60 is noteworthy.

An endometrium showing more or less marked signs of a corpus luteum effect was noted twice in women in their fifties, but in both there had been a delayed menopause. In no case was a premenstrual endometrium observed after more than one year of amenorrhea.

Hyperplasia of the endometrium, as the name is now used, is probably still applied to a somewhat heterogeneous group. In this series of cases hyperplasia was noted twice among the 13 endometrial specimens of patients under 50 years of age. These were probably instances of the typical endometrial hyperplasia of the premenopause years and fall in this group of postmenopause cases only because the definition of the menopause was a clinical one. There were 6 patients with hyperplasia in the fifties and 3 in the sixties. Of these, four were associated with a tumor of the granulosa cell group and hence easily explained. Two occurred with pseudomucinous tumors of the ovary, and although manifesting less typical changes than those associated with the granulosa cell tumors, still they were decidedly not atrophic. This hyperplasia is possibly the result of a general hyperemia in the pelvis from the presence of the tumor, possibly the result of substances elaborated by the cysts or by activated ovarian cells in the walls of the cysts. Finally there were three cases of hyperplasia with no demonstrable cause. Certain characteristics of these suggest that they may be of more neoplastic character than the hyperplasia of earlier years, and less immediately dependent upon ovarian stimuli.

In an earlier paper (Taylor) the association of hyperplasia and carcinoma of the endometrium was reported in 15 out of 34 cases of corpus carcinoma in which areas of noncancerous endometrium were available for study. Novak and Yui noted 25 such associations of

hyperplasia and carcinoma in 64 similar cases. It would be hard to imagine any other precursor to cancer of the corpus than some form of glandular hyperplasia.

CONCLUSIONS

Among 406 gynecologic cases admitted to the hospital for vaginal bleeding after the menopause, some type of malignant tumor was present in approximately 63 per cent.

Benign tumors of the uterus and ovary were the lesions chiefly responsible for the symptom in 17 per cent of the cases. Of special interest was the association of hyperplasia of the endometrium with typical cystic pseudomucinous tumors of the ovary in two instances.

Inflammatory lesions, usually in the cervix or vagina, were the apparent cause of bleeding in 11 per cent.

In the remainder, or about 8 per cent, no gross lesion to explain the bleeding was present in the pelvis. Several of this group showed evidence of a late ovarian effect on the endometrium or of an endometrial hyperplasia due to this or other causes. These instances of hyperplastic changes in the postmenopausal endometrium are important as possible precancerous lesions.

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A CHEMICAL TEST FOR PREGNANCY APPLIED TO THE DETERMINATION OF ESTRIN IN THE URINE OF NORMAL AND TOXEMIC PATIENTS IN THE LAST TRIMESTER OF PREGNANCY

II. APPLICATION OF A SHORT CHEMICAL METHOD; AND ADMINISTRATION OF THEELIN* IN LATE TOXEMIAS OF PREGNANCY

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IN A previous paper⁸ we reported results of the chemical determination of estrin in the urine during the last trimester of pregnancy from a series of 60 hospitalized patients. We were able to establish levels of estrin excretion in normal late pregnancy, and to show a definite lowering of these levels in chronic nephritis complicating pregnancy, and in pre-eclampsia.

This study was undertaken to collect more data in this field; to apply a modified chemical procedure¹⁷ for the detection of estrin; and to observe the effects of theelin administration in patients suffering from the late toxemias of pregnancy.‡

METHODS

Toxemic patients admitted to the University Hospital in the last trimester of pregnancy were studied carefully by frequent examinations of urine, blood pressure, eye grounds, blood chemistry, and kidney

*The theelin used in this investigation was provided through the courtesy of Parke, Davis and Co.

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‡The following is the classification of the late toxemias of pregnancy as accepted in our clinic: pre-eclampsia, eclampsia, and chronic nephritis complicating pregnancy.

function. Twenty-four-hour urine specimens were collected and estrin determinations made. A few normal cases (Table I) were included in order to establish normal levels of estrin excretion.

All cases of toxemia were subjected to the routine treatment of the clinic which included absolute bed rest; limitation of fluids to 1,500 c.c. per day (in the presence of edema, and unlimited fluids in its absence); low-protein salt-free diet; magnesium sulphate by mouth; and 50 per cent glucose and 10 per cent magnesium sulphate intravenously, and morphine as required in exacerbations. Other factors in treatment such as the administration of sedatives; induction of labor either medically or by amniotomy; cesarean section; and sterilization, all varied as indicated.

Only a few cases were private, the majority being service admissions from our out-patient department. Nearly all patients were given prenatal care in our clinic where they had been reporting for from two weeks to eight months previous to their admission to the hospital.

No cases of true eclampsia appear in this series, because it was impossible to obtain complete twenty-four-hour urine specimens.

No patient with pre-eclampsia from our own clinic later developed eclampsia.

TABLE I. SIX NORMAL CASES

CASE	AGE	COLOR	PARITY	DURATION OF PREG. WHEN URINE OBT. IN WEEKS	F.N.*	BABY
40	22	W	1-0-0-0†	40	101	F.T.L.*
6	32	B	3-0-0-3	40	96	F.T.L.
1	21	B	2-0-1-2	40	91	F.T.L.
42	20	B	0-0-0-0	38	87	F.T.L.
51	21	W	1-0-0-1	36	75	F.T.L.
46	34	B	10-0-1-11 (twins)	36	73	F.T.L.

*F.N., ferric chloride number; F.T.L., full-term living baby.

†The first figure represents the number of full-term children whether alive or stillborn; the second, the number of prematures; the third, the number of abortions (before the twenty-eighth week); and the fourth shows the number of living children.

PROCEDURE

A modification of the Schmulovitz and Wylie test⁹ for the chemical diagnosis of pregnancy by the detection of estrin in the urine was devised by one of us (H. B. W.). A separate publication¹⁷ is planned to describe this test in detail. Briefly, this procedure follows the principles of the original test⁹ with a few minor changes, but uses only one-tenth of the twenty-four-hour specimen. A marked reduction in the time required for the laboratory performance of this test, of from twenty-four to thirty hours to four hours, has thereby been achieved.

The essential principle of the chemical test for pregnancy "... consists in the extraction of estrin from the urine with ether and its detection by coupling with diazotized paranitroaniline to form a deep-colored azo dye. ..."

Estrin excretion is expressed in terms of the "ferric chloride number" (F.N. as shown in Tables I to V) which is obtained as follows: "... the final colored alcoholic layer containing the estrin extracted from the specimen is filtered into a colorimeter cup and set at 10 mm., and is compared with a standard 33 per cent ferric chloride solution, the reading of which is the 'ferric chloride number.'"

In this short procedure the final reading in millimeters is multiplied by 10 and the factor 9 (the blank error is 1 mm.) is subtracted to give the final "ferric chloride number" (F. N.).

Each specimen in this series was examined by the short method using the same technique throughout.

Estrin determinations were made on the specimens from the cases shown in Table V soon after admission. Similar tests were made on one-tenth of each twenty-four-hour specimen following each of 3 theelin injections (except in Case 58). The patients were carefully observed clinically to note any unfavorable reactions or any improvement in their condition which might have been attributed to theelin administration.

Goldberger⁵ has defined free and combined "estrins" according to Marrian's concept. Free "estrins" are those that can be extracted with ether from the untreated urine, and combined "estrins" are extractable with ether only after hydrolysis of the urine by acidification and boiling. Since all specimens were hydrolyzed our estimations are based on the total estrin output in twenty-four hours.¹⁷

DISCUSSION

In Tables I to III the data are arranged under the following headings: case number, age, color, parity of the patient, duration of pregnancy in weeks at the time when the twenty-four-hour specimen was obtained for analysis, "ferric chloride number" (F.N.), and the outcome of the pregnancy (F.T.L., full-term living baby; F.T.D., full-term baby who was stillborn, or born alive but did not survive the neonatal period; L, premature baby who survived the neonatal period; and D, premature baby who was stillborn, or born alive but did not survive the neonatal period).

Table IV is a summary of Tables I to III, and includes a comparison of the data of the present series of cases with those of the first series.⁸

Table V gives a summary of the data of the cases in which theelin was administered.

TABLE II. TWENTY-SIX CASES OF CHRONIC NEPHRITIS COMPLICATING PREGNANCY

CASE	AGE	COLOR	PARITY	DURATION OF PREG. WHEN URINE OBT. IN WEEKS	F.N.	BABY
31	35	W	3-0-0-3	40	63	F.T.L.
5	32	W	5-0-1-5	37	61	F.T.L.
24	36	B	2-1-0-1	30	61	F.T.L.
37	28	W	3-0-0-3	40	61	F.T.L.
53	28	B	4-4-0-4	40	61	F.T.L.
21	28	W	5-2-1-5	40	58	F.T.L.
57	31	B	4-0-2-4	38	57	F.T.L.
38	28	W	4-0-0-3	40	56	F.T.L.
22	19	B	1-0-0-1	39	55	F.T.L.
45	32	B	3-1-1-3	36	53	F.T.L.
56	30	B	2-0-1-2	38	53	F.T.L.
60	23	W	0-0-0-0	35	52	F.T.L.
3	24	B	0-2-0-0	28	51	32D*
15	19	B	0-0-0-0	34	51	34D
48	38	B	7-0-2-5	32	51	32L†
58	24	W	0-0-0-0	34	50	34L
54	28	B	2-0-0-2	38	49	F.T.L.
9	25	B	5-0-0-5	41	39	F.T.L.
16	19	B	1-1-0-2	38	40	F.T.L.
50	27	W	3-1-0-3	38	33	F.T.L.
17	24	B	0-0-0-0	40	32	F.T.L.
8	26	B	1-0-0-1	40	31	F.T.L.
18	14	B	0-0-0-0	38	31	F.T.L.
13	16	B	0-0-0-0	36	28.5	F.T.L.
7	20	W	0-0-0-0	24	23	F.T.L.
19	21	W	0-0-0-0	30	23	30L

*Weeks, dead. †Weeks, living.

Normal Cases.—The six cases shown in Table I were all normal in that they showed no clinical evidences of toxemias of pregnancy. They were admitted to the hospital near term, not in labor, for the following reasons:

Contracted pelvis	3 cases
Previous dystocia	2 cases
Recent operation for rectal stricture	1 case

One patient was a primigravida; 2 were white and 4 were colored.

The average duration of pregnancy at the time the twenty-four-hour specimens were obtained was 38.33 weeks, while the average "ferrie chloride number" (F.N.) was 87.16, the highest being 101 and the lowest 73. From Table IV we see that the average "ferrie chloride numbers" in the normal group in the first series^s and in the present series are very close, and, that in the present series the range of the "ferrie chloride number" is more restricted than in the former series, but the average is higher.

TABLE III. TWENTY-SIX CASES OF PRE-ECLAMPSIA

CASE	AGE	COLOR	PARITY	DURATION OF PREG. WHEN URINE OBT. IN WEEKS	F.N.	BABY
28	23	W	0-0-0-0	32	70	F.T.L.
33	17	B	0-0-0-0	38	56	F.T.L.
29	18	B	0-0-0-0	36	55	F.T.L.
11	16	B	0-0-0-0	37	51	F.T.L.
27	24	W	0-0-0-0	39	46	F.T.L.
30	32	B	1-0-0-1	38	43	F.T.L.
35	24	W	0-0-0-0	40	42	F.T.L.
49	21	B	0-0-1-0	40	42	F.T.L.
32	25	W	0-0-0-0	37	41	F.T.L.
39	25	W	0-0-0-0	38	41	F.T.L.
41	18	W	0-0-0-0	38	40	F.T.L.
43	20	W	0-0-0-0	39	40	F.T.L.
44	16	B	0-0-0-0	36	40	F.T.L.
55	18	W	0-0-0-0	34	40	38L
52	18	B	0-0-0-0	35	37	F.T.L.
59	21	W	0-0-0-0	39	37	F.T.L.
2	16	B	0-0-0-0	35	36	F.T.L.
12	18	W	0-0-0-0	40	36	F.T.L.
36	21	W	0-0-0-0	38	36	F.T.L.
47	15	B	0-0-0-0	28	36	F.T.L.
14	22	W	0-0-0-0	40	33	F.T.L.
4	15	B	0-0-0-0	34	31	F.T.L.
20	30	B	0-0-0-0	36	30	F.T.L.
34	38	W	0-0-0-0	40	30	F.T.L.
26	18	B	0-0-0-0	40	30	F.T.D.
25	31	W	0-0-0-0	38	22	F.T.L.

TABLE IV. SUMMARY OF TABLES I TO III. COMPARISON OF RESULTS WITH LONG AND SHORT METHOD

	AVERAGE F.N.	F.N. RANGE	TOTAL NO. OF CASES	AVERAGE DURA- TION OF PREG- NANCY, WEEKS
Normal	A* 83.30	152.00-56.60	21	36.00
	B 87.16	101.00-73.00	6	38.33
Chronic nephritis complicating preg.	A 51.67	64.00-40.00	19	37.10
	B 47.05	63.00-23.00	26	36.30
Pre-eclampsia	A 36.87	45.00-28.50	20	38.10
	B 40.03	70.00-22.00	26	37.11

*A, Series originally reported.^s B, Present series.

Cases 51 and 46 (Table I) had been diagnosed as having chronic nephritis complicating pregnancy in their previous pregnancies, but in each case the pregnancy reported here showed no toxic signs or symptoms. It may be significant that these two cases gave the lowest "ferric chloride numbers," which may have indicated some residual pathology from the toxemia in the previous pregnancy even though the present pregnancy was clinically normal.

All patients in the normal series were delivered of full-term living children who survived the neonatal period.

Chronic Nephritis Complicating Pregnancy.—The 26 cases of chronic nephritis complicating pregnancy shown in Table II were characterized by: albuminuria, nitrogen retention and elevation of blood pressure at least one month before delivery which persisted at levels above normal after delivery. Many showed edema and pathologic eye grounds. One patient (Case 56, Table II) died at home about one month after discharge from the hospital of generalized carcinomatosis which had developed from malignant breast tumor. (This patient and Case 34 [Table III] who also died, represent an uncorrected maternal mortality of 3.4 per cent for the entire series of 58 cases.) All these patients were admitted to the hospital because of toxemia. Eight were primigravidas. There is a definite increase in the number of primigravidas in this series of cases of chronic nephritis complicating pregnancy as compared to our previous series⁸ in which there was only one primigravida in 19 cases. Patients in this series had toxic symptoms and findings to a varying degree for from six weeks to six months prior to delivery. Ten patients were white and 16 were colored.

The average duration of pregnancy when the twenty-four-hour urine specimens were obtained was 36.3 weeks, while the average "ferric chloride number" (F.N.) was 47.05, the highest, 63.0, and the lowest, 23.0 (Table IV). Thus there was a wider range of F.N. and a lower average in this series than in the first (see Table IV).

In the present series there were 21 full-term living children, 32- and 34-week stillbirths, and 30-, 32-, and 34-week living babies who survived the neonatal period.

No attempt was made to subdivide these patients into those who had suffered from chronic nephritis prior to the first pregnancy or those developing chronic nephritis during the course of subsequent repeated pregnancies, nor to differentiate between the types of chronic nephritis.

Definite lowering of estrin excretion in chronic nephritis complicating pregnancy in the previous series⁸ has been confirmed in the present series as shown in Table IV.

There is, however, no overlapping of the F.N. of this group with the F.N. of the normal group as was observed in the first series. Thus the normal cases are more sharply defined from the two toxemic groups. On the other hand, there is considerable overlapping of the F.N. of the nephritic group with that of the series of cases of pre-eclampsia.

Pre-eclampsia.—Table III represents a series of 26 cases of pre-eclampsia characterized by: sudden elevation of blood pressure, sudden appearance of albumin in urine previously normal, increased uric acid retention, and by the sudden onset of subjective symptoms in late pregnancy varying from edema of the feet and ankles to edema of the face and hands, abnormal weight gain, nausea and vomiting, headache, precordial pain, and visual disturbances. These patients were admitted to the hospital because of toxemia. Only 2 of these patients were multigravidas. Fourteen patients were white, 12 were colored. The average duration of pregnancy when the twenty-four-hour urine specimens were obtained was 37.11 weeks; while the average "ferric chloride number" (F.N.) was 40.03, the highest, 70.00, and the lowest, 22.00 (Table IV).

In this series there was one full-term baby who did not survive the neonatal period, and one 38-week living baby who was discharged in good condition. The remainder of these pregnancies terminated in the births of full-term living infants, all of whom survived the neonatal period.

One patient in this series (Case 34, Table III) was an unregistered case who was admitted because of fulminating pre-eclampsia. Elective laparotrachelotomy was performed and the patient died four days later of peritonitis due to infection by hemolytic streptococci.

Two other patients in this series (Cases 26 and 55, Table III) with fulminating pre-eclampsia were delivered by elective laparotrachelotomy with good results.

Case 28 (Table III) was a primigravida admitted at the thirty-second week of her pregnancy because of a mild pre-eclampsia. The "ferric chloride number" (F.N.) was 70 at that time. On routine treatment the patient improved and was discharged. At term the patient was readmitted in active labor and gave no evidence of toxic manifestations throughout her stay in the hospital. This case is mentioned to show a mild pre-eclamptic with a "ferric chloride number" (F.N.) above the range for the remainder of the group (Table III).

We again found a definitely lowered level of estrin excretion in pre-eclampsia (Table IV). The difference between the average "ferric chloride number" (F.N.) in this group and that of the first series⁸ is not great, and there is little difference between the estrin excretion in this group of pre-eclamptic patients and the group of patients suffering from chronic nephritis complicating pregnancy (see Table IV). Therefore, using the short method, we were not able to differentiate the two groups of cases as sharply as was possible in the original study. The "ferric chloride number" range for the two groups of cases of toxemia is practically the same, while the normal group stands alone with the exception of Case 28 (Table III).

We do not claim at present, however, that it is possible with our methods to correlate the estrin excretion with the severity and type of toxemia, although it may be fair to state that it seems possible to differentiate normal pregnancy from the two pathologic groups under discussion.

Theelin Administration.—Before administering theelin to any of our patients, a very careful search of the literature was made to determine the safety of this procedure. Mazer⁶ and his co-workers, after injecting estrogenic substance in divided doses, concluded that it produced no significant changes in blood pressure, basal metabolism, body weight, blood count, and blood chemistry. Witherspoon,¹⁶ and Robinson⁷ and his colleagues found that the administration of estrin near term might or might not induce premature labor, but that it was not a reliable means of induction.

Zieman¹⁸ warns against side reactions as urticaria, generalized dermatitis, and anaphylactic shock following intragluteal injections of theelin in oil (1 c.c. containing 1000 international units). No reactions were observed in our cases.

Geschickter, Lewis, and Hartman⁴ found a depressing effect of estrin on the basal metabolic rate by administering the "estrin hormones" to patients with hyperthyroidism.

After an extensive search of the literature, Dodds² failed to find any incontrovertible evidence that estrogenic substances are carcinogenic. Discussing the relationship between estrogenic and carcinogenic substances, Frank³ states that as yet no convincing contraindications to the clinical employment of estrogenic substances have been discovered.

Steinkamm and Giesen¹⁵ observed that as yet it had not been proved that estrogenic substance reduces blood pressure. Their studies were made on nonpregnant women.

It has been suggested by Smith and Smith,¹² and Smith and Kennard¹¹ that the excessive amounts of prolan in the blood and urine of toxemic women have their origin in the placenta. Smith and Smith¹² further suggest that the continued overproduction of prolan by the placenta is a possible causal factor in the etiology of the toxemias of late pregnancy. These same authors^{13, 14} have called attention to the mutually antagonistic action of prolan and estrin and suggest estrin as an experimental therapeutic measure in these toxemias.¹⁴ At the onset of our second series of observations it was our purpose to test this action of theelin in a few cases (see Table V). Regardless of the origin of excess prolan in the late toxemias, it seemed logical to us to administer theelin in such cases, not as replacement therapy for the lowered estrin level, but to inhibit the action of excess prolan.

TABLE V. SUMMARY OF CASES IN WHICH THEELIN WAS ADMINISTERED

CASE	AGE	COLOR	PARITY	DIAGNOSIS	INTERVAL BET. LAST DOSE THEELIN AND ONSET OF LABOR	HOURS LENGTH LABOR	BABY	APPARENT EFFECT OF THEELIN ON TOXEMIA	F.N.*	THEELIN INT. U.
36	21	W	0-0-0-0	Pre-ecl.	32.50 hr.	7	F.T.L.	None	36	30,000
41	18	W	0-0-0-0	Pre-ecl.	10 days	8.5	F.T.L.	None	40	30,000
43	20	W	0-0-0-0	Pre-ecl.	31.00 hr.	15	F.T.L.	None	40	30,000
44	16	B	0-0-0-0	Pre-ecl.	24 days	14.5	F.T.L.	None	40	30,000
50	27	W	3-1-0-3	Neph.	10 days	5	F.T.L.	None	33	30,000
51	21	W	1-0-0-1	Norm.	24 days	8	F.T.L.	None	75	30,000
52	18	B	0-0-0-0	Pre-ecl.	31 days	12	F.T.L.	None	37	30,000
58	24	W	0-0-0-0	Neph.	3.00 hr.	11	34L	None	50	10,000
59	21	W	0-0-0-0	Pre-ecl.	15.50 hr.	6.75	F.T.L.	None	37	30,000
60	23	W	0-0-0-0	Neph.	30 days	4	F.T.L.	None	52	30,000

*Previous to theelin administration.

The immediate problem in the treatment of these cases was to determine what product to use and in what dosage it should be administered. Our studies were made on the output of total estrin in twenty-four hours. It was arbitrarily decided to administer a preparation of so-called "free estrins"⁵ in an oil solution to permit of gradual absorption. Urinary excretion of estrogenic substance at term in normal pregnancy has been determined by various investigators at about 6,000 rat units in twenty-four hours. Since our series of toxemic patients in the last trimester of pregnancy excreted approximately only one-half the normal amount (Table IV) it was decided to administer 3,000 rat units of estrogenic substance per day for three successive days. Larger doses were decided against to avoid the possibility of exaggerating existing symptoms, because the tolerance of these patients to this substance was unknown. Shute,¹⁰ in treating cases of late toxemia with estrin, observed a picture strongly suggestive of abruptio placentae in one of his patients following estrin administration. He therefore suggests that during pregnancy estrin should be used quite cautiously and in small dosage. Shute administered massive doses of estrogenic substances.

Theelin was used in this investigation (1 c.c. ampoule containing 10,000 international units which is approximately 3,000 Doisy rat units).

The cases chosen for hormone therapy (Table V) were not especially selected from among the others. One normal case was included for comparison (Case 51, Table V).

Nine of the 10 ward cases shown in Table V were given 10,000 international units of theelin intramuscularly on 3 successive days (30,000 international units in all), while the patient in Case 58 received only one injection of 10,000 international units since labor began three hours later. All patients given theelin were kept on the routine treatment except that oral administration of magnesium sulphate was discontinued in order that accurate twenty-four-hour urine specimens could be collected.

The injections were given intragluteally followed by several minutes of gentle massage. None of the patients complained of pain or discomfort other than that caused by the entrance of the needle or by the pressure of the injection, both of which were momentary. No side reactions were observed. The patients were given to understand that these injections were a part of the routine treatment.

The cases were carefully observed for blood pressure changes at least every four hours (except the patient in Case 51 who was normal), and by frequent eye

ground, blood chemistry, kidney function, and urine examinations. The general condition and the progress were also carefully noted.

Eight of these patients were white while 2 were colored. Eight were primigravidas. Six were pre-eclamptic, 3 were noted as having chronic nephritis complicating pregnancy, and 1 was normal.

The latent period between the last injection of theelin and the onset of labor varied from three hours (Case 58, Table V only 1 injection given) to thirty-one days. Only 4 of these patients went into labor before ten days following the last injection, and in these the hormone possibly may have had some part in the induction. In 2 cases (Cases 50 and 51) it was necessary to induce labor by amniotomy.

The longest labor in the series was fifteen hours, the shortest, four hours, while the average was 9.17 hours. From our data it is impossible to state definitely whether or not the theelin influenced the length of labor, but it is interesting to note the short average duration of labor, even in this small series, especially since 8 of the 10 patients were primigravidas.

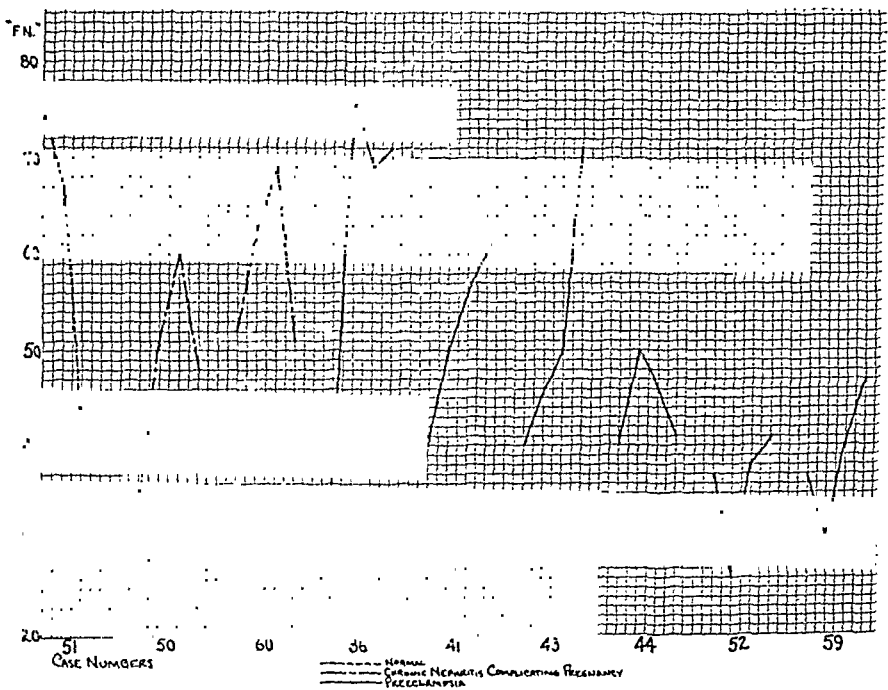


Chart 1.—Estrin excretion.

All but one of the patients in this series were delivered of full-term living children who survived the neonatal period. The patient in Case 58 was delivered of a thirty-four-week premature baby who survived the neonatal period. No untoward effects of the theelin upon any of these babies were noted.

There was no delay in uterine involution in any of these patients, nor was there any acceleration in this process.

After reviewing these cases critically we cannot say that there was any improvement in any of the 10 patients which could be ascribed directly to the hormone therapy. It is possible that the short average duration of labor may have been the result of this therapy. Failure to observe clinical improvement may have been due to inadequate dosage or to too late administration. The possible advantages of administering theelin to patients with decreasing estrin excretion before clinical manifestations of toxemia appear should certainly be kept in mind.

Chart 1 shows individual curves representing the estrin excretion of the 9 patients each of whom received 3 theelin injections. The first reading in each curve is the "ferric chloride number" (F.N.) obtained from examination of a twenty-four-hour specimen before hormone therapy was instituted, while the other three points in each curve represent the "ferric chloride numbers" (F.N.) of twenty-four-hour speci-

pregnancy is sufficient to suggest, if not prove the solution," he says. "Whether the individual inquiry approaches the problem biologically, statistically, clinically or, say, physiologically, it is at once apparent that, with few exceptions, the usual and average study proceeds from fallacious premises, gratuitous assumptions, and almost complete lack of definition and limitation of terms; and that from so unstable a foundation it limps through a morass of slipshod data and the crudest handling of evidence to a palpably questionable conclusion. . . . Certainly it were anything but scientific to lay to *pregnancy*, in a woman who has tolerated her pregnancy extremely well, an activation or aggravation of her tuberculosis that followed an abnormal, exhausting or dangerous second stage of labor (as has frequently happened). . . . But, greater than any other fallacy in the customary approach to the problem of 'pregnancy and tuberculosis' is the almost universal premise and assumption that pregnancy acts as a 'constant' factor in whatever influence it may have on tuberculosis. That is to say, that all women tolerate pregnancy alike, which means nothing else than that the bodily economy of every woman reacts to pregnancy in the same way. Extensive reading would indicate that practically every author on the subject takes this most important datum for granted, notwithstanding its obvious falsity. Indeed, at the moment the writer cannot recall a study of 'tuberculosis and pregnancy' in which the author even casually suggested that pregnancy can act differently in different women or even differently in the same woman as one pregnancy follows another. . . . The most elementary practice soon teaches the observing physician that the bodily response of womankind to pregnancy is of almost 'infinite variety.' . . . And it would seem that any study or discussion concerning the influence of pregnancy on tuberculosis would have to take these facts into account. . . . Even pseudoscience flies out the window when we are obliged to draw our conclusions from the data of ages lumped together, of non-discrimination between the variables of reproductive history of women undergoing observation and study, and so forth. . . . In summary, then, what are the known *facts*? They are, first, that pregnancy operates in widely divergent fashion on non-tuberculous women, that is, it may uplift and it may depress the individual economy; second, that pregnancy works to similar effect in tuberculous women, that is, it may rouse and it may quiet active tuberculosis. . . . Why, then, this pother and uncertainty? For any difference of opinion could be concerned only with what might be called quantitative effects, that is: Does pregnancy harm the tuberculous woman more frequently than it benefits her; and, if so, how much more? Before attempting to answer a problem, so insoluble on the basis of the data at hand, the writer begs permission to make a suggestion, as perhaps worthy of consideration in attempting a solution. He would put this in the form of a question, as follows: May it not be that pregnancy exerts a harmful effect on tuberculosis in those women who, without tuberculosis, would naturally tolerate pregnancy poorly, and a harmless or even beneficial effect on those tuberculous women who, without tuberculosis, would stand pregnancy well or even have their bodily economy improved by pregnancy?"

The present study was undertaken¹ to determine in what percentage of married women of childbearing age admitted to the Trudeau Sanatorium with active pulmonary tuberculosis the onset of the disease or its reactivation could be shown to bear a possible relation of a preceding pregnancy, and (2) to study the subsequent course of this group in comparison with a second group in similar age brackets manifesting pulmonary lesions of like extent. For this purpose the records of the Sanatorium from 1916 through 1935 (comprising approximately 5,000 admissions) were examined and the histories of the 457 married women between the ages of 20 and 35 (inclusive) set aside for study. In this group 6 cases were found to present incomplete data and were discarded, leaving a total of 451 cases for analysis.

The age group of 20 to 35 was chosen arbitrarily as covering the period of maximum childbearing. For the purposes of this study, pregnancies terminated either spontaneously or artificially in the first trimester (in most instances interruptions occurred in the first 8 to 10 weeks of gestation) were ignored as being unlikely to have an influence on either the onset or reactivation of the tuberculosis.

The 451 cases were divided into 6 categories as follows: (1) those who had had no viable pregnancies, (2) those who had had a full-term or viable pregnancy more than six months before the onset of the tuberculosis, (3) those who dated the onset of their tuberculosis from labor, (4) those who were pregnant when their tuberculosis was diagnosed but who continued to term, (5) those in whom a tuberculous process appeared within six months of the termination of a viable or full-term pregnancy, and (6) those who had become pregnant after the onset of tuberculosis. These groups, for the purposes of this study, may be combined under 3 large headings: (A) those who had had no viable pregnancies or a viable pregnancy more than six months before the onset of tuberculosis, who may be considered the controls, (B) those whose onset of tuberculosis bore some relation to a pregnancy, and (C) a small group who had been pregnant since tuberculosis had been diagnosed. The distribution of cases in each group, the extent of the disease on admission to the Sanatorium, and the mortality from tuberculosis in each group is shown in Table I.

TABLE I

	NO. OF CASES	PER CENT OF TOTAL	EXTENT OF DISEASE AND MORTALITY DUE TO TUBERCULOSIS IN EACH GROUP*					
			MIN.	DEAD %	M.A.	DEAD %	F.A.	DEAD %
No full-term or viable pregnancies	204	45.2	45	8.8	113	17.7	25	40.0
Full-term or viable pregnancy more than 6 months before onset of tuberculosis	159	35.2	29	10.3	97	17.5	19	57.9
Total controls	363	87.0	74	9.4	210	17.6	44	50.0
Full-term or viable pregnancy less than 6 months before onset of tuberculosis								
1. Onset tubere. dated from pregnancy	22	4.8	3	0	18	16.6	0	0
2. Pregnant at onset of tuberculosis	16	3.5	5	0	9	33.3	2	100.0
3. No relation except time	16	3.5	0	0	9	11.1	5	40.0
Total	54	12.0	8	0	36	19.4	7	59.1
Pregnant since onset of tuberculosis	34	7.5	7	0	20	25.0	4	50.0

*Min., minimal; M.A., moderately advanced; F.A., far advanced.

The division of each group according to the extent of the pulmonary lesions on admission to the Sanatorium, using the classification of the National Tuberculosis Association, and the end results in each class are shown in Table II. Because of the small number of cases in certain of the subgroups, no attempt was made to express the mortality in percentages.

An analysis of the survival rates for five, ten, and fifteen years in each group is given in Table III. Here again percentages are omitted except in those groups

TABLE II

	MINIMAL				MODERATELY ADVANCED				FAR ADVANCED			
	ALIVE	DEAD OF TUBERCULOSIS	DEAD OF NON-TUBERCULOUS CAUSES	NO FOLLOW-UP	ALIVE	DEAD OF TUBERCULOSIS	DEAD OF NON-TUBERCULOUS CAUSES	NO FOLLOW-UP	ALIVE	DEAD OF TUBERCULOSIS	DEAD OF NON-TUBERCULOUS CAUSES	NO FOLLOW-UP
No full-term or viable pregnancy	10	4	1	6	92	20	1	15	13	10	1	0
Pregnant more than 6 months before onset of tuberculosis	26	3	0	2	76	17	4	12	7	11	1	0
Onset of tuberculosis dated from full-term or viable pregnancy	3	0	0	0	15	3	0	0	0	0	0	1
Pregnant at onset of tuberculosis	5	0	0	0	6	3	0	0	0	2	0	0
No relation except a full-term or viable pregnancy within 6 months of onset of tuberculosis	0	0	0	1	7	1	1	1	3	2	0	0
Pregnant since onset of tuberculosis	7	0	0	2	15	5	0	1	2	2	0	0

TABLE III. SURVIVAL RATES

		5 YEARS			10 YEARS			15 YEARS		
		NO. CASES	SURVIVED	PER CENT	NO. CASES	SURVIVED	PER CENT	NO. CASES	SURVIVED	PER CENT
No full-term or viable pregnancies	Min.*	30	27	90.0	16	14	87.5	9	7	77.7
	M.A.	77	61	79.2	37	26	70.2	15	9	60.0
	F.A.	16	9	56.3	7	2	28.5	5	1	20.0
Pregnant more than 6 months before onset of tuberculosis	Min.	18	17	94.4	8	6	75.0	8	5	62.5
	M.A.	74	63	85.1	47	35	74.5	21	9	42.4
	F.A.	15	7	46.6	9	2	22.2	5	0	0
Onset tuberculosis dated from full-term pregnancy or labor	Min.	2	2		1	1		0	0	
	M.A.	16	13	82.2	13	10	76.9	6	3	50.0
	F.A.	0	0		0	0		0	0	
Pregnant at onset of tuberculosis	Min.	4	4		2	2		1	1	
	M.A.	6	4		2	1		0	0	
	F.A.	2	0		2	0		1	0	
No relation noted except a pregnancy within 6 months of onset of tuberculosis	Min.	0	0		0	0		0	0	
	M.A.	5	4		5	4		5	4	
	F.A.	3	2		2	0		1	0	
Pregnant since onset of tuberculosis	Min.	5	5		2	2		2	2	
	M.A.	15	11	73.3	9	5	55.5	3	1	33.3
	F.A.	3	1		1	0		0	0	

*Min., minimal; M.A., moderately advanced; F.A., far advanced.

showing a sufficient number of cases to make such figures significant or indicative of trends. These data, under the two large headings of those patients who were nulliparas or whose pregnancy probably bore no relation to the onset of the tuberculosis and those in whom such a relationship might be shown to have existed, are summarized in Table IV.

Table V shows the type of onset in each group.

TABLE IV

		5 YEARS			10 YEARS			15 YEARS		
		NO. CASES	SUR- VIVED	PER CENT	NO. CASES	SUR- VIVED	PER CENT	NO. CASES	SUR- VIVED	PER CENT
Control Group	Min.*	48	44	91.6	24	20	83.3	17	12	70.6
	M.A.	151	122	82.1	84	61	72.6	36	18	50.0
	F.A.	31	16	51.6	16	4	25.0	10	1	10.0
Group with pregnancy relationship	Min.	6	6	100.0	3	3	100.0	1	1	
	M.A.	27	21	77.7	20	15	75.0	11	7	63.6
	F.A.	5	2	40.0	4	0	0	2	0	0

*Min., minimal; M.A., moderately advanced; F.A., far advanced.

TABLE V. TYPE OF ONSET OF TUBERCULOSIS

	PLEURITIC		INSIDIOUS		CATARRHIAL		HEMOPTOIC		PNEUMONIC	
	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT	NO. CASES	PER CENT
<i>Pregnancy Group (54 Cases)</i>										
Onset tuberculosis dated from pregnancy	1	4.5	13	59.0	4	18.1	4	18.1		
Pregnant at onset of tuberculosis	3	18.7	7	43.7	3	18.7	3	18.7		
Pregnancy within 6 months of onset of tuberculosis	3	18.7	6	37.5	5	31.2	1	6.2	1	6.2
Total	7	13.0	26	48.1	12	22.2	8	14.8	1	1.8
<i>Control Group (350 Cases)</i>										
No full-term or viable pregnancies	28	14.4	80	41.2	71	36.6	14	7.2	1	0.5
Full-term or viable pregnancy more than 6 months from onset of tuberculosis	24	15.3	64	41.0	57	36.5	11	7.0		
	52	14.8	144	41.1	128	36.5	25	7.2	1	0.2

While not pertinent to the purposes of this study, it is interesting to note that in this group the parity of the patient seemed to bear no relation to the extent of the pulmonary disease on admission to the Sanatorium. Specifically, of the 28 primiparas, there were 5 with minimal, 19 with moderately advanced, and 4 with far-advanced lesions. There were 4 deaths among the primiparas, of which 2 occurred in patients admitted with moderately advanced disease and 2 in patients classed as far advanced. Of 13 secondiparas, there were 2 minimals, 9 moderately advanced, and 2 far-advanced cases with 3 deaths: 2 in the moderately advanced group and 1 in the far advanced. Of 10 patients who had had more than 2 children on admission, there was 1 minimal, 8 moderately advanced, and 1 far-advanced case with 4 deaths, of which 3 occurred in women with moderately advanced lesions on admission and 1 in a patient with far-advanced disease.

In the patients who had become pregnant after the diagnosis of tuberculosis had been made there were 16 primiparas of which 5 had minimal, 8 moderately advanced, and 3 far-advanced lesions. In this group, 2 patients with moderately advanced and 2 with far-advanced cases died of tuberculosis. Of 12 secondiparas there were 2 minimals, 9 moderately advanced, and 1 far-advanced cases with 3 deaths in the group with moderately advanced lesions. And finally, 3 patients who had had more than 2 children were all classed as moderately advanced on admission and no deaths occurred in the group. Data obtained from the records on the health of the babies born of the pregnancies which appeared to be related to the onset of the tuberculosis are difficult to evaluate as the condition of the offspring was not given in 9 instances. Three babies are known to have died as follows: 1 stillbirth, 1 neonatal death on the second day, and 1 death from status lymphaticus at an unknown age. All the other children were noted as being in good health. Of the children born to patients after tuberculosis had been diagnosed, data on 2 were omitted from the records, 1 was recorded as being in "fair" health, 27 in good health, and 4 dead of the following causes: 1 neonatal death (this was the second child of this patient who had died within a few days of birth), 1 of malnutrition at $3\frac{1}{2}$ years of age, 1 of meningococcic meningitis at 8 years of age, and 1 of unknown cause.

DISCUSSION

While it is only fair to point out that this study is based upon a selected group in that (1) only "favorable" cases are admitted to the Trudeau Sanatorium and (2) the cases came for the most part from an economic stratum financially able to receive treatment in a private sanatorium and, hence, a group which would be expected to carry out, at least in modified form, a proper regime for their tuberculosis on returning to their homes, it would appear that the end results are not materially affected by a preceding pregnancy. This, it would seem, is the important point to determine in attempting to evaluate the influence of a pregnancy on the end-results of a tuberculous lesion which it might have been a factor in aggravating. With such results in a group that has received adequate, or at least six months', treatment for tuberculosis is one justified in considering the group in whom the end results have not been so favorable, not because of a pregnancy, but because they failed to receive proper treatment for their tuberculosis? Any attempt to evaluate the influence of the physiologic functions of gestation, parturition and the puerperium on pulmonary tuberculosis which is not properly treated must be considered of dubious value as ample experience with the untreated disease shows a high mortality of itself.

Similarly, one must exclude as falling into the category of untreated or inadequately treated cases those whose economic conditions necessitate their leaving the sanatorium before the "cure" is complete to return to their homes and assume the burden of a household and a child. While the importance of this factor is not underestimated, it must be looked upon as a "side effect" of childbearing and not the act itself in considering its effect on tuberculosis. In other words, one must distinguish between the influence of *pregnancy*, and its accompanying labor and puerperium (for the three are divisible only in theory), and *childbearing* on pulmonary tuberculosis. This study would indicate that probably 12 per cent of *untreated* cases of latent tuber-

culosis in women of the childbearing age are reactivated or aggravated by gestation and its sequelae. Figures are not available by which this number can be compared with a similar group of *treated* cases; a limited personal experience, however, agrees with the findings of Alice Hill and others that reactivation or aggravation of properly treated cases occurs in a negligible proportion, especially when effective collapse therapy is instituted.

CONCLUSIONS

1. Of 451 married women between the ages of 20 and 35 inclusive who were admitted to the Trudeau Sanatorium between 1916 and 1935, approximately 12 per cent showed a possible relationship between the onset of their tuberculosis and a preceding viable pregnancy. In 3.5 per cent the symptoms first appeared during gestation and in 4.8 per cent the tuberculosis dated from parturition.

2. There is a slight tendency for the groups showing a relationship between the onset of the tuberculosis and pregnancy to exhibit more advanced types of lesions of admission to the Sanatorium. This does not, however, mean that the lesions manifested by this group tended to be more "acute" or show a higher incidence of exudative processes than those presented by the controls. While this finding may be interpreted as evidence of an unfavorable influence of pregnancy on a tuberculous process, it also suggests that with more careful examination of the lungs during the prenatal period many of these cases might have been diagnosed before symptoms appeared and proper *preventive* treatment instituted before the disease became activated.

3. There is no significant difference in the death rate from tuberculosis in the patients in whom the onset of the disease is related to a full-term or viable pregnancy as compared with that of a group of nulliparas of the same age group who show lesions of similar extent.

4. There is a relatively high incidence of hemoptoic onset of pulmonary tuberculosis in the group whose disease appears to bear a relationship to a gestation or parturition. While interesting in the light of the increased capillary permeability known to exist during pregnancy, the true significance of this observation is difficult to explain at the present time.

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THE EFFECT OF ESTROGENIC HORMONE UPON THE CONTRACTILITY OF THE FALLOPIAN TUBES*

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ALTHOUGH the hormonologic physiology of the uterine musculature has been the subject of intensive investigation by numerous workers, there is very little in the literature on the subject of the hormonal control of the Fallopian tubes. Because of certain clinical conditions related to tubal function (ectopic gestation and possibly, also, some forms of sterility and dysmenorrhea), it was felt desirable to determine the relationship of the Fallopian tubes to the various hormones which normally exercise a physiologic influence on the female gonads and genital tract.

The literature dealing with uterine musculature is extensive and the views held by different investigators are frequently contradictory (see Reynolds' review).¹ However, certain observations are generally agreed upon.

Athias² pointed out in 1919 that uterine motility is controlled by the ovaries. He demonstrated in guinea pigs that following castration, rhythmic spontaneous motility of the uterus is lost, but that motility could be restored in the ovariectomized animals by ovarian grafts. Similar views were held by Loewe³ and Marshall.⁴ Corner⁵ gives Blair⁶ credit for first reporting a relationship between uterine contractility and the estrus cycle. Blair noted that the contraction waves produced by a strip of uterine muscle immersed in Locke's solution varied at different points of the cycle. The rate was lowest at the time of estrus, increasing gradually to a maximum rate in the resting stage and decreasing at proestrus. Keye⁷ working in Corner's laboratory confirmed and amplified the work of Blair. By means of "in vitro" experiments employing a segment of sow's uterus suspended in physiologic salt solution, he observed that when the strip of uterine muscle was taken from a sow killed during estrus, the contractions were large and slow. During the first few days following ovulation, the contractions became more rapid and less ample, and at the tenth day they were occurring at a rate of eight per minute. Similar changes in motility were established in a variety of laboratory animals, all having cyclic ovarian activity. Frank, Bonham and Gustavson⁸ were able to demonstrate "in vitro," contractions characteristic of the estrus phase, in spayed rats which had previously been injected with estrogen extracts. Similar results (indicating that the estrogenic hormone will induce or augment uterine contractions) were obtained by numerous investigators.⁹⁻¹⁶

The fact that the ovaries control uterine motility in animals and that cyclic variations in this motility occur dependent upon the growth and development of the graafian follicle, was thus established by means of "in vitro" and "in vivo" experiments in animals.

*Presented at a meeting of the New York Obstetrical Society, October 12, 1937.

In human beings, Knaus¹⁷ has demonstrated regular uterine contraction waves in normal cyclic females and that these contractions tended to disappear at the time when the corpus luteum was presumed to be at the height of its activity. Moir¹⁸ obtained recordings of human uterine contractions by introducing into the uterus a small rubber bag connected with a Hurthle manometer. He found that the contractions were frequent, of small amplitude and regular during the first half of the menstrual cycle, but after the sixteenth day they became progressively stronger. Applying the technic of Moir to the puerperal uterus, Falls, Lackner and Krohn¹⁹ demonstrated marked increase in uterine contractions following the administration of estrogenic hormone.*

That the Fallopian tubes are capable of muscular contractions was first pointed out by Kehrer.²⁰ He demonstrated kymographic recordings of contraction waves in isolated strips of excised tube. Seckinger²¹ observed that the tubal contraction waves varied at different phases of the estrus cycle. He found two types of contraction waves, the first, consisting of a regular rhythm at the rate of four to six per minute, was present at all times of the cycle except for a few days before and after ovulation. During estrus, the rate became much more rapid (ten to fifteen per minute) with an alternation of groups of small and large excursions. Seckinger and Corner²² observed somewhat similar variations in the contractions of segments of the Fallopian tubes of monkeys at different stages of the menstrual cycle. Wislocki and Guttmacher²³ were able to demonstrate tubal contractions by immersing the intact uterus and tubes of pigs in oxygenated Locke's solution.

Interest in the physiology of the Fallopian tubes was given a fresh impetus following the introduction of transuterine tubal insufflation by Rubin^{24, 25} to determine the patency of the tubes. During the insufflation procedure, he observed that in patent tubes, variations occurred in the manometric pressure readings. Rubin subsequently demonstrated by means of kymographic recordings that these fluctuations were caused by tubal peristalsis. He furthermore established the fact that the contractions in normal unobstructed tubes produced a characteristic series of fluctuations on the kymograph. In women in the pre- and postclimacteric states, the tubal contractions were greatly diminished.

EXPERIMENTAL STUDY

We have undertaken to determine the effect exercised by the various hormones involved in the human cycle upon the motility of the Fallopian tubes. The problem of graphically recording tubal contractions was solved very simply by employing the transuterine tubal insufflation method of Rubin as it is used clinically in the study of sterility. Although the apparatus is primarily employed for the determination of patency of the Fallopian tubes, tubal contraction waves are automatically recorded in cases with normal unobstructed Fallopian tubes (Fig. 1). This method has the advantage of being performed with no risk and very little discomfort to the patient.

In the present investigation, it was planned to study the effect of an estrogenic principle of proved clinical efficacy upon the contractility of the Fallopian tubes. As experimental material, a group of women who were considered on clinical grounds to have very little or no ovarian activity was chosen from our Menopause Clinic. The women had all

*Since the completion of this paper, Krohn, Lackner, and Soskin (*Am. J. Obst. & Gynec.* 31: 279, 1937) have reported the results of their studies on the effect of ovarian hormones on the nonpuerperal human uterus. To record uterine contractions they introduced a rubber balloon into the uterus and connected it to a recording device. They found that in normal patients the motility of the uterus varies at different periods of the menstrual cycle, the contractions being most marked in the first day of menstruation. Increase in the intensity and frequency of the contractions occurred following the administration of estrogenic substance, but after progesterone the motility was decreased.

ceased to menstruate and had symptoms characteristic of marked ovarian deficiency (hot flushes, weakness, headaches, and dizziness). It was felt that, if the ovarian estrogenic factor normally influenced tubal contractility, one would expect to find marked diminution in the tubal contractions in this group. Furthermore, if marked decrease in tubal contractility were proved in these cases, this group would constitute excellent experimental material upon which to test the ability of an estrogenic substance to restore normal tubal activity. The patients were insufflated and recordings made of the tubal contractions. They were then given a course of estrogenic hormone (estradiol-benzoate, progynon B)* injections and at the end of the period of treatment the insufflation was repeated, kymographic records being again made of the tubal contractions.

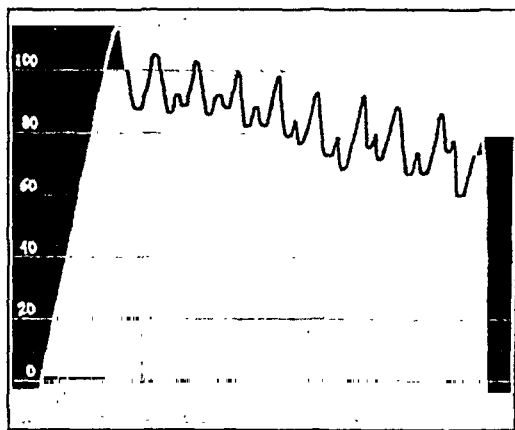


Fig. 1.—Normal tubal contractions in a woman with regular menstrual cycle.

In addition to the clinical evidence of ovarian deficiency, it was felt desirable to have some objective method of estimating the degree of estrogen deficiency and the response to the estrogen hormone. For this purpose the cytology of the vaginal secretions was studied in each case. Papanicolaou and Shorr²⁶⁻²⁸ have shown that the human vaginal smear after the menopause exhibits certain well-defined cytologic characteristics indicative of ovarian deficiency, and that following the administration of adequate amounts of estrogen the smear resembles that of a female with normally functioning ovaries. Salmon and Frank²⁹ suggested a classification of the human smears into four groups to parallel the grading of rodent smears. In the present study, this classification was employed to indicate approximately the relative degrees of estrogen deficiency before treatment and the response to the injected estrogenic hormone.

EXPERIMENTAL PROCEDURE

Recording of Tubal Contractions.—The Rubin apparatus³⁰ was employed using the usual technic for insufflation. One hundred and fifty to 180 c.c. of carbon-

*We wish to express our thanks to Dr. Gregory Stragnell and Dr. Irwin Schwenk of the Schering Corporation of Bloomfield, New Jersey, for their kindness in supplying us with the progynon B employed in this study.

dioxide gas is introduced into the uterine cavity through a cannula which is connected with a mercury manometer and a kymograph. The pressure at which the gas enters the abdomen and the tubal contractions are recorded on the drum. In these patients, two or three preliminary recordings were taken, a week apart.

Estrogen Administration.—After the last preliminary insufflation, the patients were given a series of intramuscular injections of estradiol-benzoate in sesame oil (Progynon B—10,000 international units per c.c.). The total dosage varied from 120,000 to 650,000 international units given in divided doses over a period of ten to fourteen days at intervals of two to three days. After the last injection, a recording was made of the tubal contractions and repeated a week later.

Vaginal Smear Technic.—Vaginal smears were obtained by aspirating the surface secretion from the vaginal fornices with a glass pipette. The secretion was then diluted with saline and spread on a glass slide. The smear is then allowed to dry, stained with aqueous fuchsin for one minute, and washed with tap water. Vaginal smears were taken before the preliminary insufflation and twice weekly during the course of injections with progynon-B, and at the completion of the estrogen treatment.

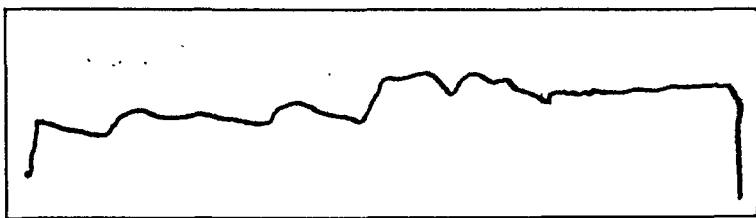


Fig. 2.—Case 1. Preliminary insufflation showing few irregular weak contractions.

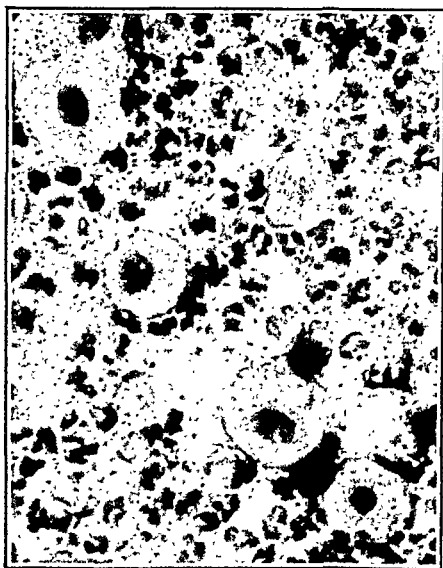


Fig. 3.

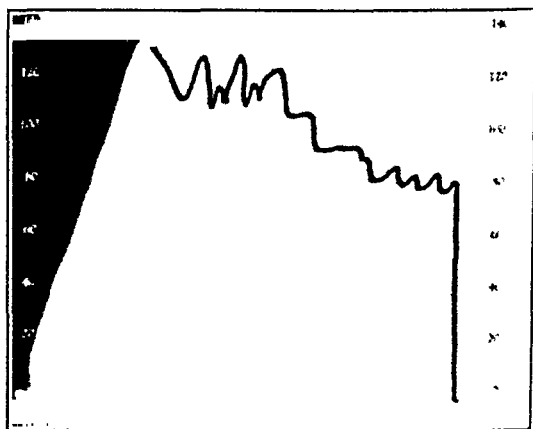


Fig. 4.

Fig. 3.—Case 1. Preliminary vaginal smear. Preponderance of leucocytes and "compact cells" indicative of estrogen deficiency. (Reaction I.)

Fig. 4.—Case 1. Tubal contractions after 120,000 I.U. of progynon-B. Note increased amplitude and frequency of contractions in contrast with preliminary recording (Fig. 2).

CASE HISTORIES

CASE 1.—In patient M. P., aged 48 years, a natural menopause occurred two years before this investigation. The preliminary insufflation was performed on June 27, 1936. The carbon dioxide passed through at a pressure of 25 mm. of mercury.

Irregular contraction waves of low amplitude were recorded (Fig. 2). The preliminary vaginal smear taken at this time exhibited a typical negative phase characterized by a preponderance of leucocytes with some scattered oval epithelial ("compact cells") cells containing large nuclei (Fig. 3). The patient was then given 190,000 international units of progynon-B during a period of two weeks. On the day following the last injection, insufflation was again performed (Fig. 4).

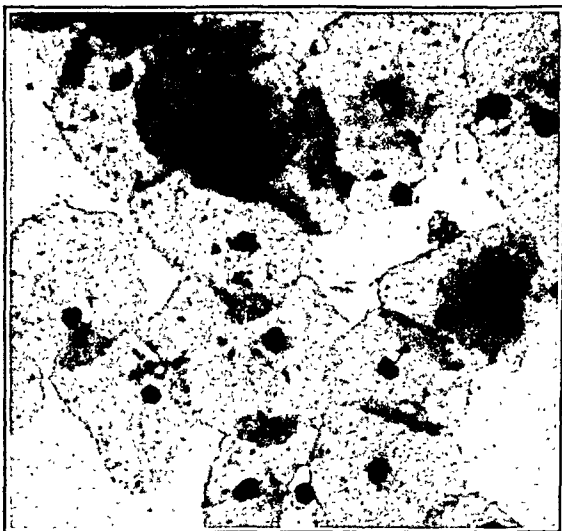


Fig. 5.—Case 1. Vaginal smear taken after estrogen therapy. Leucocytes and "compact cells" replaced by squamous epithelial cells, characteristic estrogenic effect. (Reaction IV.) Compare with preliminary smear (Fig. 3).

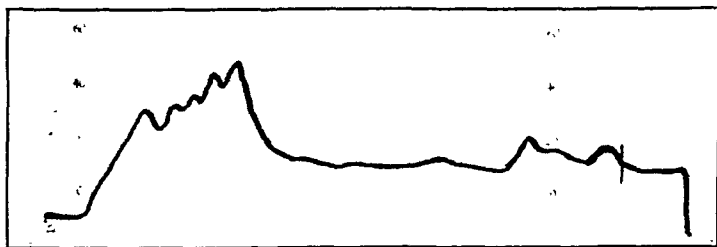


Fig. 6.—Case 2. Preliminary insufflation showing weak irregular contractions at low pressure.

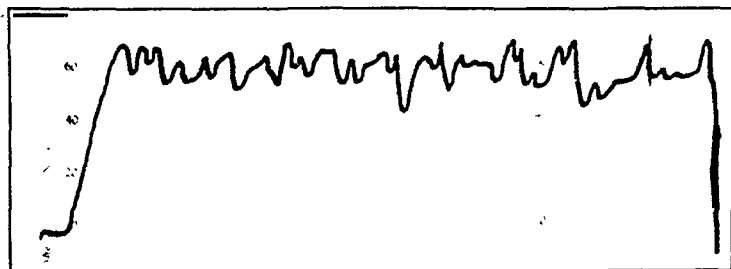


Fig. 7.—Case 2. Tubal contractions after 190,000 I.U. of progynon-B. Note frequent contraction waves of good amplitude at pressure of 55 to 70 mm. of mercury.

The pressure rose to 135 mm. of mercury and more or less regular contractions of moderate amplitude were recorded. A vaginal smear (Fig. 5) at this time exhibited a typical estrogenic effect characterized by the absence of leucocytes and "compact cells" and their replacement by large epithelial cells with small nuclei (Reaction IV).

CASE 2.—In this patient, I. G., aged 42 years, natural menopause occurred ten months before. The preliminary insufflation was performed on Feb. 1, 1936 with a maximum pressure of 50 mm. of mercury. After several weak initial contractions were recorded, the pressure dropped to 15 mm. of mercury (Fig. 6). The preliminary vaginal smear exhibited numerous nucleated oval cells and absence of cornified epithelial cells (Reaction II); 190,000 international units of progynon-B were then administered during eight days. Posttherapy insufflation was performed on the day of the last injection. Numerous contraction waves of good amplitude at a pressure of 55 to 70 mm. of mercury were recorded (Fig. 7). The vaginal smear at this time showed a complete estrogen effect. A third insufflation was performed seven days later. The contraction waves at this time were at low pressure (20 to 30 mm. of mercury), fewer in number, and irregular (Fig. 8).

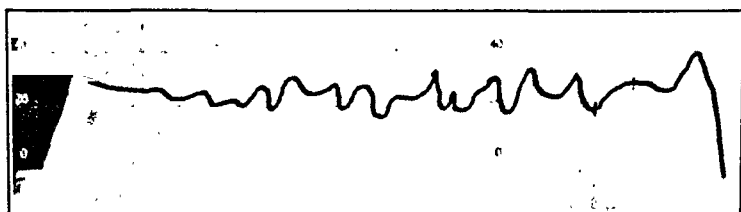


Fig. 8.—Case 2. Insufflation performed one week after cessation of therapy. Contractions are less regular, less frequent, and at reduced pressure.

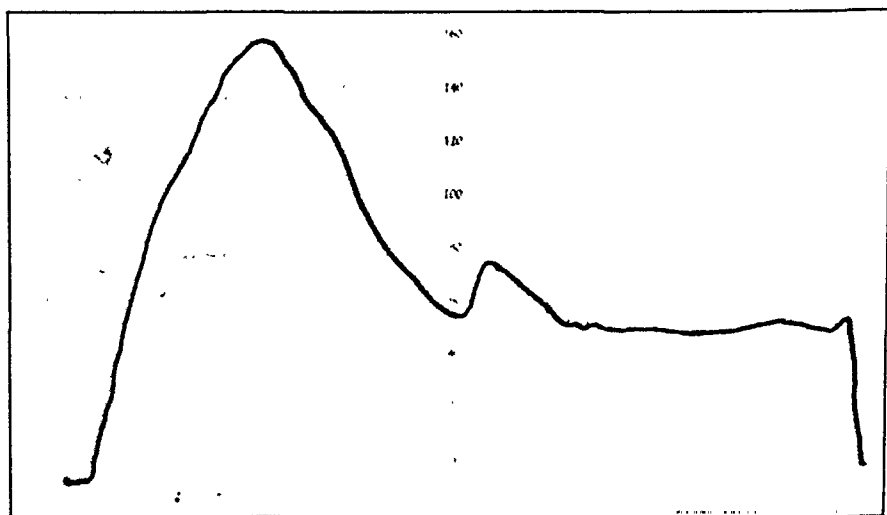


Fig. 9.—Case 4. Preliminary insufflation. No tubal contractions recorded.

CASE 3.—E. L., aged 52 years. X-ray castration was performed sixteen months before the present investigation. Four preliminary insufflations were performed at intervals of one week. In all, a few irregular contraction waves of low amplitude were recorded at the beginning. This was followed by a complete disappearance of fluctuations. The preliminary vaginal smear revealed a Reaction II, characteristic of estrogen deficiency. 190,000 international units of progynon-B were administered during seven days and insufflation was performed on the day of the last injection. The contraction waves recorded, though irregular, were of increased frequency and amplitude. The pressure however remained, for the most part, at a low level (20 to 40 mm. of mercury). The vaginal smear at the completion of the injections revealed a definite estrogen effect. Another insufflation was performed nine days later and revealed shallow, irregular contractions.

CASE 4.—M. S., aged 47 years, had a natural menopause of two years' duration. The preliminary insufflation on June 6, 1936 revealed an initial pressure rise to 160 mm. of mercury which became stabilized quickly at 55 mm. No contraction waves were recorded (Fig. 9). The preliminary vaginal smear contained leucocytes and compact cells (Reaction II). The patient was given 190,000 international units of progynon-B during the following nine days. Insufflation performed the day after the last injection revealed the following: the pressure rose to 115 mm. of

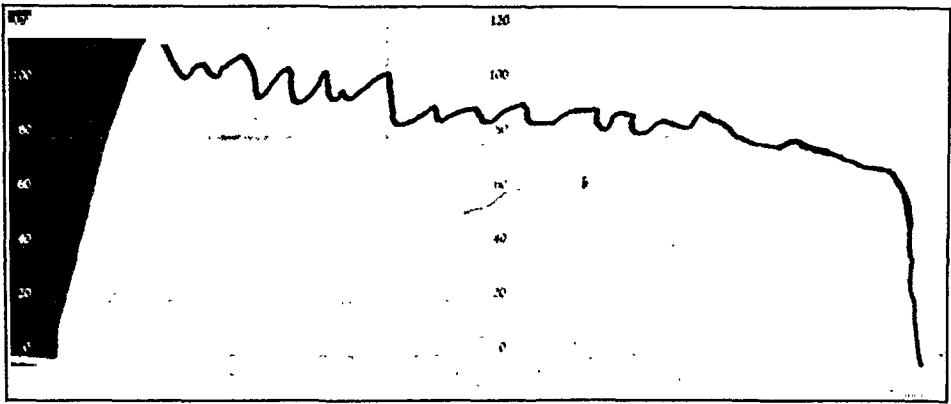


Fig. 10.—Case 4. Insufflation after 190,000 I.U. of progynon-B, showing numerous contraction waves at raised pressure level.

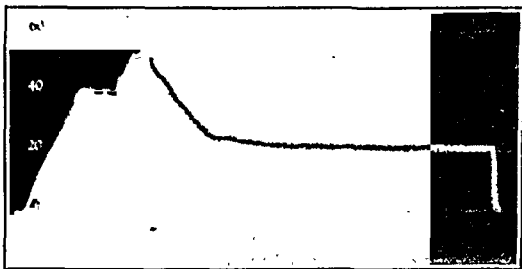


Fig. 11.



Fig. 12.

Fig. 11.—Case 5. Preliminary insufflation. Note total absence of tubal contractions.

Fig. 12.—Case 5. Preliminary vaginal smear. Predominance of leucocytes associated with numerous "compact cells" indicating marked estrogen deficiency. (Reaction I.)

mercury and more or less regular contraction waves were recorded at pressures varying between 80 and 110 mm. of mercury (Fig. 10). The posttherapy vaginal smear revealed a characteristic estrogen response.

CASE 5.—L. W., aged 51 years, had a natural menopause eleven years before. The preliminary insufflation was performed on March 6, 1937. The initial pressure rose to a maximum of 55 mm. of mercury and dropped quickly to 20 mm. of mercury with a total absence of contraction waves (Fig. 11). The vaginal smear exhibited a completely "negative" phase (Fig. 12) characterized by a predominance of

leucocytes together with numerous "compact cells." A total of 650,000 international units of progynon-B was given over a period of seven days. Posttherapy insufflation performed the day of the last injection revealed the following: the pressure rose to 95 mm. of mercury; regular contraction waves of high amplitude were recorded at pressures varying from 60 to 90 mm. of mercury (Fig. 13). The vaginal smear at this time showed full estrogen effect (Reaction IV) (Fig. 14). Insufflation was repeated sixteen days later. The pressure rose to a maximum of 35 mm. of mercury

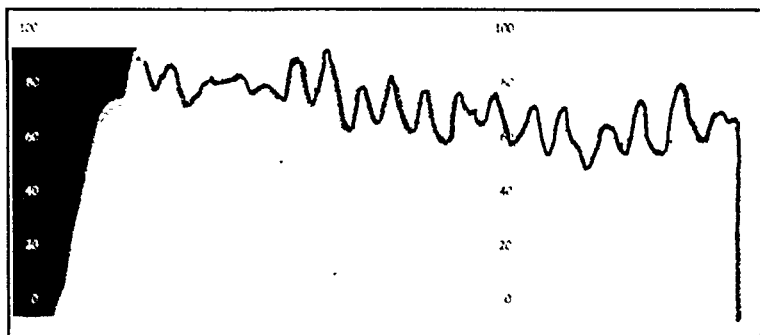


Fig. 13.—Case 5. Insufflation after 650,000 I.U. of progynon-B. Frequent, regular contraction waves of high amplitude at increased pressure. Compare with Fig. 11.

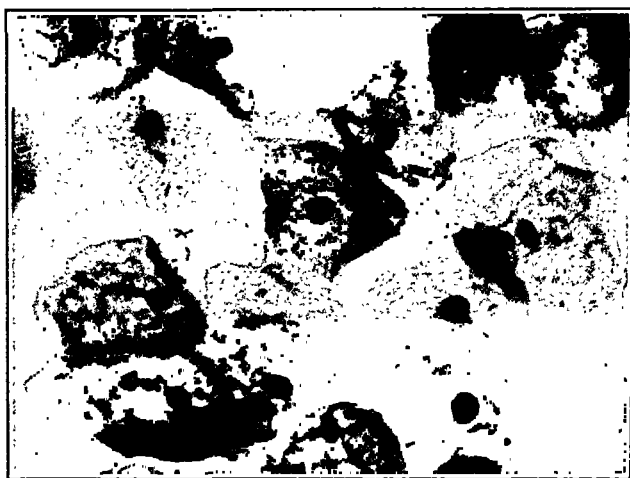


Fig. 14.—Case 5. Vaginal smear after 650,000 I.U. of progynon-B exhibiting strong estrogenic effect.

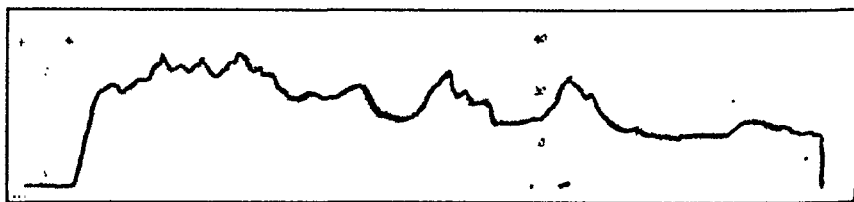


Fig. 15.—Case 5. Insufflation performed sixteen days after the last injection of estrogen. Contraction waves are irregular, of low amplitude, and recorded at low pressures (15 to 35 mm. of mercury). The effect of the injected estrogen has almost completely worn off.

and irregular contraction waves of low amplitude were recorded at pressures varying between 15 and 30 mm. of mercury (Fig. 15). The vaginal smear at this time still exhibited a moderate estrogen effect (Reaction III).

CASE 6.—C. H., aged 27 years. Menopause induced by x-ray four and one-half years before the present investigation. The preliminary insufflation was performed on April 4, 1936. The pressure rose to a maximum of 65 mm. of mercury. The

contraction waves were somewhat irregular but of fair amplitude. The preliminary vaginal smear revealed numerous epithelial cells of various sizes with occasional leucocytes and no cornified epithelial cells; 120,000 international units of progynon-B were administered during twelve days. The post-therapy insufflation was performed two days after the last injection and revealed regular contraction waves of good amplitude at a pressure of 45 to 60 mm. of mercury. The vaginal smear at this time exhibited full estrogenic effect. In this case, there was apparently some residual ovarian function in spite of the amenorrhea of four and one-half years' duration. This is indicated by the vaginal smear and accounts for the presence of tubal contraction waves in the pretreatment recording.

RESULTS

During the preliminary period, all cases showed definite diminution in tubal contractility. This was manifested by a total absence of contractions in some cases and in others by a markedly reduced amplitude as well as irregularity in the fluctuations. The recordings were also at low pressure. In most cases, after the introduction of the gas, several contraction waves were recorded which were irregular and of low amplitude. Thereafter, the contraction waves disappeared entirely. Apparently, the Fallopian tubes respond at first to the irritation caused by the gas with some weak, irregular contractions. The vaginal smears showed definite deficiency of estrogenic hormone in all the cases studied. In the older patients, those who were longest past the menopause, the smears exhibited the most regressive changes (leucocytes and compact cells) indicative of marked estrogen deficiency.

After the administration of the estrogenic hormone, increase in tubal contractility was noted. This was evidenced by the appearance of frequent, regular, rhythmic contraction waves of high amplitude at a heightened pressure level. Coincident with this striking change in the tubal motility, a definite change occurred in the vaginal smears, all of which exhibited characteristic estrogenic effects. It was noted that in the instances in which the smears exhibited the least regressive changes before treatment, the preliminary insufflation revealed some tubal contraction waves. This was interpreted as indicating that some estrogenic hormone was still being produced, even though the patient was no longer menstruating.

DISCUSSION

Although one would be inclined to assume from the observations made by numerous investigators on the subject of uterine contractility that the estrogenic hormone is responsible for the normal muscular contractions of the tubes, as well as the uterus, no direct experimental evidence had been submitted in support of such an idea. Rubin had observed diminished motility at the menopause and normal motility in some cases of prolonged amenorrhea. However, it must be conceded that clinical observations without parallel hormone studies are by themselves too inconsistent to permit of the formulation of a coordinated theory as to the relationship of ovarian function to tubal contractility.

In the cases studied in this investigation it was assumed on the basis of clinical criteria (amenorrhea, flushes, etc.), that the ovaries were

either not functioning at all or at a markedly reduced level. This was borne out by the vaginal smears which exhibited definite estrogen deficiency. In all of these cases there was striking evidence of marked decrease in tubal contractility as shown by the recording of few contraction waves of low amplitude or of none at all. Following the administration of the estradiol-benzoate, normal tubal peristalsis was restored as evidenced by the recording of regular, rhythmic contraction waves of high amplitude.

The striking change in the vaginal smears in each case which coincided with the return of tubal motility proves beyond question that the same hormonal factor, which is "estrogenic" (as shown by the vaginal reaction), will also initiate and maintain normal tubal peristalsis.

On the basis of these observations, the question arises as to whether tubal contractility may not be impaired in some patients whose ovarian function is subnormal. Furthermore, one must consider the possibility that such impairment of tubal motility may be the etiologic factor responsible for some types of sterility and tubal pregnancy.

SUMMARY AND CONCLUSIONS

1. It appears from this study that, after the menopause, with the gradual cessation of the production of estrogenic hormone, there is marked impairment of tone of the musculature of the Fallopian tubes and gradual disappearance of the regular rhythmic tubal peristalsis. This is demonstrated clearly in kymographic records by the reduced resistance to the entry of the gas and by the disappearance of regular rhythmic contraction waves. The most striking impairment of motility was observed in the cases longest after the menopause. In the recent cases, evidence of residual ovarian function was manifested by irregular contraction waves of low amplitude at low pressure.

2. Coincident with the impairment in tubal contractility, the vaginal smears exhibit signs of various degrees of estrogenic hormone deficiency. The most marked deficiency occurring in the patients showing least tubal activity.

3. Administration of estrogenic hormone in the form of the estradiol-benzoate (progynon-B) resulted in the development of rhythmic contraction waves of high amplitude, similar to those observed in normal females with functioning ovaries.

4. Coincident with the reappearance of tubal contractions, the vaginal smears showed full estrogen effects.

5. The striking restoration of regular tubal contractions in these cases parallel with the marked estrogenic effect manifested in the vaginal smears following the administration of the estradiol-benzoate indicates that in the human female the ovarian estrogenic hormone is responsible for the production of the normal rhythmic tubal contractions.

6. The possibility that impairment of tubal contractility due to estrogen deficiency may play a role in some forms of sterility and tubal pregnancy is suggested.

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THE NONPROTEIN, UREA, AND REST NITROGEN OF THE BLOOD DURING LABOR AND THE PUERPERIUM

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THE puerperium is a period of readjustment. The marked physiologic and anatomical changes which have occurred during pregnancy realign themselves at this time to normal nonpregnant conditions. It is necessary to know when and how these changes occur. Some take place immediately after delivery, others require days and sometimes weeks or even months before the truly normal nonpregnant conditions prevail.

In order to know whether the puerperium is actually following a normal course, it is necessary to know the normal limits. A great amount of work has been done on the chemistry of pregnancy and the puerperium but, as far as we can ascertain, no one has made a detailed study of the nonprotein and urea nitrogen of the blood during the puerperium.

In an earlier paper we presented our findings for normal pregnancy. They confirmed the work of other investigators, notably Williams, and Bunker and Mundell. We found that the nonprotein nitrogen decreases during the first six months of pregnancy from the average nonpregnant value of approximately 30, to 24 mg. per 100 c.c. of blood. During the last four months of pregnancy the nonprotein nitrogen

increases steadily to a value of 26 mg. at term and on the eighth day postpartum it averages 33 mg. per 100 c.c. of blood. The urea nitrogen diminishes during the first six months to a value of 6 mg. per 100 c.c. of blood and then maintains a constant level until the eighth or ninth month, when it begins to rise, having an average value of 7.2 mg. at term and 11 mg. per 100 c.c. of blood on the eighth day post partum.

We also pointed out that, due to the fact that the nonprotein nitrogen falls and rises more rapidly than the urea nitrogen, the rest nitrogen decreases during the first six months of pregnancy to a value of 18 mg. per 100 c.c. of blood and then increases during the latter part of pregnancy, being 19.2 mg. at term. It is further increased during the first week of the puerperium, reaching a value of 21.4 mg. on the eighth day post partum.

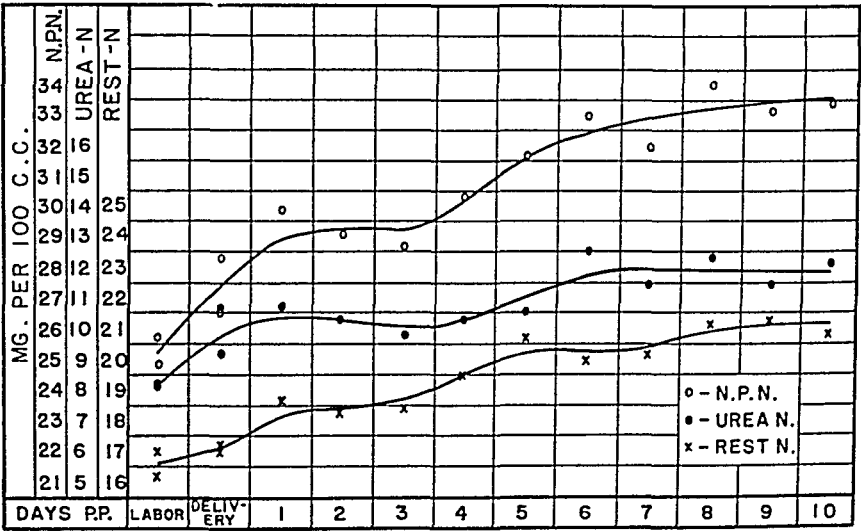


Fig. 1.—A graph illustrating the average values for nonprotein nitrogen, urea nitrogen and rest nitrogen of the blood during labor, immediately following delivery and during the first ten days of the puerperium.

At the time that paper was written, we had only a few analyses during labor and therefore did not emphasize our results. Now, however, we have made a study of 40 patients. Blood was obtained during the first stage of labor and immediately following delivery. These same patients also were studied during the puerperium. They were divided into two groups and blood was obtained from each group on alternating days; that is, from 20 patients, blood was drawn on the first, third, fifth, seventh, and ninth days post partum, while in the other group blood was drawn on the "even" days for ten days. The prime purpose for such a procedure was the comfort and convenience of the patients. It should be noted, however, that the curve in Fig. 1 has been drawn in respect to both groups, and therefore should be the same as that obtained if we had taken blood from each of the 40 patients every day.

METHODS

Filtrates prepared from whole blood by the procedures of Somogyi and Folin-Wu were used for the determination of urea nitrogen and nonprotein nitrogen, respectively. Urea nitrogen was determined by the manometric hypobromite method of Van

Slyke and Kugel. The method of Folin and Wu was used for the determination of nonprotein nitrogen. The rest nitrogen was calculated as the difference of the two.

By the term "rest" nitrogen we mean all the nonprotein nitrogen of the blood, excepting the urea nitrogen, in contradistinction to "undetermined" nitrogen which not only excludes urea nitrogen but also amino, uric acid, creatine, and creatinine nitrogen.

NONPROTEIN NITROGEN

According to Fig. 1 there is an increase during labor of approximately 2 mg. nonprotein nitrogen per 100 c.c. of blood, the average value during the first stage

TABLE I. NONPROTEIN NITROGEN

CASE	LABOR	AFTER DELIVERY	FIRST DAY	THIRD DAY	FIFTH DAY	SEVENTH DAY	NINTH DAY
1	31.6	28.0	34.1	23.6	29.4	28.7	32.6
2	26.0		29.4	30.6	31.6	31.1	34.3
3	27.1		28.6	30.4	26.0	35.5	40.0
4	24.6	21.9	30.2	29.2	30.2	31.6	33.5
5	23.2	28.8-		28.3	30.3	29.1	31.6
6	28.6	28.2	30.3	29.8	30.8	28.7	28.8
7	24.8	31.4	28.2	32.2	30.8		
8	19.7	25.1	24.7	25.3	30.8	26.2	27.4
9	24.2	48.0	48.8	33.7	29.8	31.1	39.7
10	23.9	23.1		27.4	30.2	30.2	34.7
11	27.8	24.7		26.3	35.7	40.2	42.9
12	26.2	28.8	29.1	25.5	33.7	38.7	37.5
13	21.8	24.9	27.8	30.9	31.9	33.3	33.3
14	33.7	36.0	33.1	35.1	36.2	34.7	35.3
15	28.0	27.6	29.2	32.4	34.3	32.8	32.8
16	26.1	29.4	25.6	28.7	27.9	36.0	30.9
17	23.0	30.6		24.7	34.5	30.2	32.6
18	24.2	25.9	30.6	30.3	25.1	34.3	31.4
19	35.1		30.6	33.3	41.9	33.7	34.3
20	25.1	26.7	26.7	29.7	31.9	33.3	27.4
Average	26.2	28.8	30.4	29.2	32.2	32.5	33.7

TABLE II. NONPROTEIN NITROGEN

CASE	LABOR	AFTER DELIVERY	SECOND DAY	FOURTH DAY	SIXTH DAY	EIGHTH DAY	TENTH DAY
21		29.4	32.6	28.0	33.5	36.4	33.7
22	35.6	24.4	30.2	33.0	37.3	34.9	38.0
23	23.1		25.6	29.6	33.1	33.1	33.3
24	21.8	23.9	30.4	30.8	33.3	34.5	33.7
25	22.3	24.6	24.8	33.3	37.7	33.1	34.5
26	25.6	26.2	26.1	26.1	32.2	34.9	40.2
27	21.9	27.9	26.7	26.8	33.7	32.2	27.9
28	24.0	25.3	30.9	28.2	29.8	31.7	29.6
29	26.2	37.3	29.4	27.0	32.2	31.7	32.8
30	22.9	25.1	26.9	26.0	29.1	26.2	29.6
31	24.7	22.1	26.7	28.8	36.0	35.7	35.3
32	29.6		30.9	40.5	34.7	38.0	36.4
33	20.8	24.3	34.9	37.3	39.7	40.5	36.4
34	27.4	27.2	33.9	34.9	34.9	32.2	33.0
35	28.4	30.8	29.6	37.7	34.1	42.9	37.0
36	23.5	28.2	30.2	37.3	32.4	41.1	36.4
37	26.2	29.2	24.9	31.9	30.9	34.5	41.6
38	33.0	34.3	40.8	30.3	37.3	32.1	27.8
39	24.2	23.1	26.4	25.9	32.2	32.6	30.6
40	19.8	22.3		24.2	26.9	31.6	30.6
Average	25.3	27.0	29.6	30.9	33.5	34.5	33.9

TABLE III. UREA NITROGEN

CASE	LABOR	AFTER DELIVERY	FIRST DAY	THIRD DAY	FIFTH DAY	SEVENTH DAY	NINTH DAY
1	8.7	8.9	9.7	8.1	9.9	9.6	8.7
2	8.8		11.4	13.0	11.8	9.1	12.4
3	7.1		8.7	10.4	10.4	13.5	12.3
4	12.0	7.5	10.3	9.3	8.4	10.1	10.1
5	9.0	10.5		11.2	10.4	11.0	10.2
6	9.9	13.7	13.9	10.3	9.3	9.7	8.5
7	7.0	11.3	9.8	9.9	10.2	11.7	
8	5.4	9.3	9.5	7.6	11.1	8.4	7.8
9	8.2	25.6	28.0	12.2	9.3	11.4	17.8
10	5.8	8.5		10.4	11.5	12.6	13.0
11	8.5	7.5		8.2	13.5	14.5	13.8
12	10.1	9.3	7.0	9.1	12.3	14.9	13.9
13	7.0	8.4	8.0	11.8	12.0	13.3	13.1
14	12.3	15.7	11.9	14.0	12.8	12.5	13.2
15	9.2	9.5	10.9	14.1	12.9	13.2	14.0
16	10.9	12.6	10.5	8.2	8.9	10.8	10.4
17	8.7	12.6		8.9	9.7	12.7	10.5
18	5.7	10.2	12.9	10.1	9.7	11.7	11.5
19	13.5		10.4	11.4	14.2	12.9	14.2
20	5.8	7.5	6.6	8.6	10.6	11.8	10.2
Average	8.7	11.1	11.2	10.3	11.0	11.8	11.9

TABLE IV. UREA NITROGEN

CASE	LABOR	AFTER DELIVERY	SECOND DAY	FOURTH DAY	SIXTH DAY	EIGHTH DAY	TENTH DAY
21		7.6	9.5	10.2	15.3	12.9	12.5
22	15.2	8.8	11.8	13.8	14.2	14.6	14.0
23	7.8		10.4	10.1	12.9	10.7	10.9
24	8.6	7.6	10.3	13.6	13.3	14.7	13.0
25	6.7	6.8	11.2	12.7	18.2	14.2	15.8
26	10.6	11.1	9.0	8.7	12.2	14.5	12.3
27	7.3	8.6	9.6	8.2	11.5	9.4	9.0
28	7.1	8.0	9.7	7.6	9.5	9.2	9.6
29	9.6	12.8	10.6	13.8	11.1	11.9	10.8
30	6.2	10.0	9.5	9.1	10.0	9.5	11.6
31	7.6	8.3	8.8	11.0	12.7	13.6	13.8
32	9.6		11.6	14.4	17.1	16.6	16.7
33	7.5	8.1	14.7	15.2	18.0	17.5	15.4
34	10.8	10.5	13.2	14.0	13.0	12.6	12.6
35	11.4	11.8	11.3	11.6	14.3	14.7	14.6
36	5.9	6.8	11.1	10.6	10.0	12.2	11.2
37	7.7	11.8	8.6	8.4	12.6	11.9	12.7
38	11.4	12.6	13.8	9.3	12.4	12.5	11.1
39	8.0	9.5	10.2	8.9	10.1	11.4	11.8
40	5.3	7.7		6.8	11.3	11.3	13.2
Average	8.6	9.5	10.8	10.9	13.0	12.8	12.6

of labor being 25.7 mg. and immediately after delivery 27.9 mg. per 100 c.c. of blood. Although this may seem as a very slight increase it may be noted that it is actually a rise of 8.6 per cent. Moreover a study of the individual cases in Tables I and II shows that only 8 of the entire series show an actual decrease, while all of the others either remain at approximately the same value or show a marked increase.

On the first day post-partum there is a further increase to an average value of 29.5 mg. This is followed by a period in which the curve levels off for about two days. From the third day until the tenth day the nonprotein nitrogen steadily increases until it has reached a value of 33.1 mg. per 100 c.c. of blood.

TABLE V. REST NITROGEN

CASE	LABOR	AFTER DELIVERY	FIRST DAY	THIRD DAY	FIFTH DAY	SEVENTH DAY	NINTH DAY
1	22.9	19.1	24.4	15.5	18.5	19.1	23.9
2	17.2		18.0	17.6	19.8	22.0	21.9
3	20.0		19.9	20.0	25.6	20.0	27.7
4	12.6	14.4	19.9	18.9	21.8	21.5	23.4
5	14.2	18.3		17.1	19.1	18.1	21.4
6	18.7	14.5	16.4	19.5	21.5	19.0	20.3
7	17.8	20.1	18.4	19.9	22.0	19.1	
8	14.3	15.8	15.2	17.7	19.7	17.9	19.6
9	16.0	22.4	20.8	21.5	20.5	19.7	21.9
10	18.1	14.6		17.0	18.7	18.6	21.7
11	19.3	17.2		18.1	22.2	25.7	29.1
12	16.1	19.5	22.1	16.4	21.4	23.8	23.6
13	14.8	16.5	19.8	19.1	19.9	20.0	20.2
14	21.4	20.7	21.2	21.1	23.4	22.2	22.1
15	18.8	18.1	18.3	18.3	21.4	19.6	18.8
16	15.2	16.8	15.1	20.5	19.0	25.2	20.5
17	14.3	18.0		15.8	24.8	17.5	22.1
18	18.5	15.7	17.7	20.2	15.4	22.6	19.9
19	21.6		20.2	21.9	27.2	20.8	20.1
20	19.3	19.2	20.1	21.1	21.3	21.5	17.2
Average	17.5	17.7	19.2	18.9	21.2	20.7	21.8

TABLE VI. REST NITROGEN

CASE	LABOR	AFTER DELIVERY	SECOND DAY	FOURTH DAY	SIXTH DAY	EIGHTH DAY	TENTH DAY
21		21.8	23.1	17.8	18.2	23.5	21.2
22	20.4	15.6	18.4	19.2	23.1	20.3	24.0
23	15.3		15.2	19.5	20.2	22.4	22.4
24	13.2	16.3	20.1	17.2	20.0	19.8	20.7
25	15.6	17.8	13.6	20.6	18.5	18.9	18.7
26	15.0	15.1	17.1	17.4	20.0	20.4	27.9
27	14.6	19.3	17.1	18.6	22.2	22.8	18.9
28	16.9	17.3	21.2	20.6	20.3	22.5	20.0
29	16.6	24.5	18.8	13.2	21.1	19.8	22.0
30	16.7	15.1	17.4	16.9	19.1	16.7	18.0
31	17.1	13.8	17.9	17.8	23.3	22.1	21.5
32	20.0		19.3	26.1	17.6	21.4	19.7
33	13.3	16.2	20.2	22.1	21.7	23.0	21.0
34	16.6	16.7	20.7	20.9	21.9	19.6	20.4
35	17.0	19.0	18.3	26.1	19.8	28.2	22.4
36	17.6	21.4	19.1	26.7	22.4	28.9	25.2
37	18.5	17.4	16.3	23.5	18.3	22.6	28.9
38	21.6	21.7	27.0	21.0	24.9	19.6	16.7
39	16.2	13.6	16.2	17.0	22.1	21.2	18.8
40	14.5	14.6		17.4	15.6	20.3	17.4
Average	16.7	17.5	18.8	20.0	20.5	21.7	21.3

Before going further it should be pointed out again that we believe that the smoothed curve is a better index of the true average than any individual point which represents an average of 20 cases. We shall therefore use the points intercepted by the curve as the average value for the 40 cases rather than the average obtained in each group of 20 cases.

UREA NITROGEN

During the first stage of labor we find the blood urea concentration to be 8.6 mg. per 100 c.c. of blood. Immediately following delivery we find that the average

value has been increased to 10.3 mg. This is an increase of 1.7 mg. per 100 c.c. of blood or in terms of percentage, 20 per cent. An inspection of Tables III and IV shows that in all of the cases excepting 5 there is either a very definite increase of the urea nitrogen concentration of the blood by the time of delivery or that it has remained the same as it was during the first stage of labor.

On the first day post partum there is a slight increase. This is followed by a leveling off or slight decrease for the next two days after which it increases to a level of about 12.4 mg. per 100 c.c. of blood, at which it remains from the sixth to the tenth day.

REST NITROGEN

There is a slight net increase in the concentration of rest nitrogen during labor. During the first stage of labor we find it to average 17.1 mg. per 100 c.c. of blood while immediately after delivery it is 17.6 mg. During the first day post partum there is a further increase followed by a fairly steady rise until the tenth day post partum, at which time the average value is 21.7 mg. per 100 c.c.

DISCUSSION

In our paper on the nonprotein, urea, and rest nitrogen of the blood during pregnancy we reported that on the eighth day post partum the average nonprotein nitrogen value was 33.1 mg. and the urea nitrogen value was 11.4. We had at that time only 15 cases, but in the present series of 40 cases we have obtained a figure of 33.7 mg. for the nonprotein nitrogen and 12.4 mg. for the urea nitrogen. The urea nitrogen figure for the present series is somewhat higher but the nonprotein nitrogen is practically identical.

Since there is a definite increase of the nonprotein nitrogen during the puerperium, it would be of interest to know what nitrogenous substances may be responsible for this rise. According to Fig. 1 the nonprotein nitrogen is increased during the puerperium from the initial values of 25.7 mg. obtained during the first stage of labor, to 34.0 mg. per 100 c.c. of blood on the tenth day post partum. This is a net increase of 8.3 mg. During this same period the urea nitrogen has increased from 8.6 mg. to 12.4 mg. a net increase of 3.7 mg. In other words 44.6 per cent of the increase of the nonprotein nitrogen can be accounted for by the increase of the urea nitrogen. Likewise the increase of the rest nitrogen is 4.6 mg. or 55.4 per cent of the increase of the nonprotein nitrogen.

In respect to this increase of the rest nitrogen we have also obtained the glutathione content of these bloods and the figures indicate that the increase of glutathione during the puerperium can account for 20 per cent of the rest nitrogen or 11.1 per cent of the nonprotein nitrogen. A résumé of the findings then shows that the increase of urea nitrogen accounts for 44.6 per cent, glutathione nitrogen 11.1 per cent, and the rest nitrogen (excluding the glutathione nitrogen) 43.3 per cent of the total increase of nonprotein nitrogen.

Although the literature has been searched, we have been unable to locate any publication in which a detailed study has been made of the

nonprotein and urea nitrogen during the puerperium. There are, however, some isolated values with which we can compare our figures.

For example Williams reports the average nonprotein nitrogen for the tenth day post partum as 33.6 mg. and the urea nitrogen as 12.9 mg. She also states that the average value for the nonprotein two or more months after confinement is 32.9 mg. with an urea nitrogen of 12.6 mg. In another report in which she confined herself to a study of the changes during labor she concluded that there is an appreciable rise in the blood urea and nonprotein nitrogen during labor in normal cases. She asserts that the urea nitrogen increases from 8.9 at the beginning of labor to 13.2 mg. per 100 c.c. of blood at the end of labor.

Caldwell and Lyle report the nonprotein nitrogen for primiparas as 26.7 and for multiparas as 29.4 mg. per 100 c.c. of blood at the end of delivery. The urea nitrogen for primiparas they report as 10.8 mg. while the average value for multiparas is 11.9 mg. Slemons and Morriss found the nonprotein nitrogen in 35 cases to average 25.2 mg. with the urea nitrogen averaging, for 12 cases, 10.5 mg. per cent at the time of delivery.

In comparing our figures with those of the above authors we find that the figures which Williams reports for the tenth day post partum are practically identical to ours. Those of Caldwell and Lyle are likewise of the same magnitude as those reported by us for the period immediately following delivery. The nonprotein nitrogen value reported by Slemons and Morriss is somewhat lower than our average, but on the other hand their average for blood urea nitrogen is similar to ours.

In our study of the changes during labor we confined ourselves to the net changes occurring between the first stage of labor and immediately after delivery. Siedentopf went one step further and made a detailed study of the changes of the nonprotein nitrogen during the various stages of labor. He divided labor into three parts as follows: Stage I, dilatation and the longest part of the second stage. Stage II, the last minutes of expulsion. Stage III, the third stage of labor. The investigation included only absolutely normal parturients who received no medicine or anesthesia of any kind. In Stage I a marked increase of nonprotein nitrogen took place in most of the cases. During Stage II the rise predominated. A decrease occurred in most of the cases during the placental period. A very marked increased was noted again in the puerperium.

From this discussion one may conclude that the nonprotein and urea nitrogen of the blood is definitely increased during labor. According to Siedentopf there is not only a net increase of the nonprotein nitrogen during labor but there are marked changes during the various periods of this process. Furthermore the increase in the nonprotein and urea nitrogen which is initiated during labor continues during the puerperium until normal nonpregnant values are reached approximately by the tenth day. While we cannot state conclusively that the cause of the changes which we have observed is a process of dehydration of the blood, we believe that probably a concentration of the blood does play some part in these changes particularly those occurring during labor.

CONCLUSIONS

1. During labor the nonprotein nitrogen of the blood is increased from an average value of 25.7 mg. to 27.9 mg. per 100 c.c. of blood. This is an increase of 8.6 per cent.

2. During the puerperium there is a steady increase of the nonprotein nitrogen. On the tenth day the average value is 34.0 mg. per 100 c.c. of blood. The net increase is 8.3 mg. or in terms of percentage 32 per cent.

3. The blood urea nitrogen is increased during labor from an average value of 8.6 mg. during the first stage of labor to a value of 10.3 mg. per 100 c.c. of blood immediately following delivery, an increase of 20 per cent.

4. The concentration of the urea nitrogen is further increased during the puerperium. It attains a value of 12.4 mg. on the sixth day post partum and maintains this level until the tenth day. In other words, the concentration of blood urea has been increased 44 per cent during the puerperium.

5. The rest nitrogen of the blood increases only slightly during labor. The average for the first stage of labor is 17.1 and immediately following delivery 17.6 mg. per 100 c.c. of blood.

6. After steadily increasing during the puerperium, the rest nitrogen attains an average value of 21.7 mg. per 100 c.c. of blood on the tenth day post partum.

7. The increase of urea nitrogen accounts for 44.6 per cent, glutathione nitrogen 11.1 per cent, and rest nitrogen (excluding glutathione nitrogen) 43.3 per cent of the increase of 8.3 mg. of nonprotein nitrogen between the time of the first stage of labor and the tenth day of the puerperium.

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From the experimental data presented it seems that introduction of the male hormone into the blood stream of the female causes an upset in her sexual cycle. The ovaries are stimulated to a precocious and prolonged production of follicles which degenerate within the gland, with the result that no luteal tissue is formed.

Since none of these female mice developed mammary tumors, it seems reasonable to assume that proliferation and change to malignancy in the mammary glands may be due, in some measure, to the luteal fraction of the ovarian hormone.

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GYNECOLOGIC FEATURES OF CARCINOMA OF THE LARGE BOWEL

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THE gynecologist can usually determine with great accuracy the pathologic nature of any gross changes in the female generative organs after a routine abdominal and vaginal examination. In recent years his proficiency in clarifying organic changes has been greatly enhanced by the application of modern instrumental and x-ray methods for exploring the uterine cavity and its adnexa. Recent advances in endocrinology have also helped to recognize the nature of functional disorders of the female generative organs.

The experienced gynecologist has long recognized the fact that pathologic disorders in any organ in close proximity to the reproductive organs may simulate some primary disease in the uterus or adnexa and give rise to a confusing clinical picture. The senior author has seen two cases of regional ileitis operated upon for a suspected twisted ovarian cyst; in another patient a sacral kidney was mistaken for a fibroid; two other patients were operated upon for fibroids and found to have a lymphosarcoma of the small intestine. An appendicular abscess not infrequently presents clinical features resembling a tuboovarian abscess. Such errors are not at all uncommon.

We have observed several cases of carcinoma of the large bowel below the sigmoid simulating pathologic disorders of the uterus or adnexa. This paper is a brief report of 9 such instances found in a series of 125 cases of carcinoma of the colon and rectum, an incidence of 7.2 per cent. This study is in no sense a critical analysis but is designed to caution the gynecologist, and even the surgeon, that a carcinoma of the bowel particularly in the region between the sigmoid and the rectum, may simulate the clinical and physical features of uterine and adnexal disease.

A brief consideration of some of the pathologic features of carcinoma of the colon and rectum will help to appreciate the mode of production of certain clinical manifestations which lead to the interpretation that one is dealing with a gynecologic disorder.

The two most common types of carcinoma found in our series of cases are the infiltrating annular carcinoma which is more frequently found in the region between the upper ascending colon and the rectosigmoid junction, and the bulky cauliflower or polypoid type found more commonly in the cecum and the rectum. In the first type there is a great tendency to bowel obstruction, while in the second hemorrhage is a common feature. In both there is a pronounced tendency

to ulceration; this ulceration may be superficial or involve the entire wall particularly in the stenosing form. Secondary infection occurs and may play a prominent rôle in the sequence of pathologic events and clinical manifestations. Ulceration permits organisms to escape into and beyond the bowel wall and thus give rise to an acute inflammation of the bowel wall. If the infection passes beyond the confines of the bowel a large inflammatory mass may form.

In two-thirds of the cases analyzed, the location of the carcinoma was between the sigmoid and rectum. One can readily appreciate how a growth in the sigmoid or rectosigmoid which has a wide range of mobility because of a long mesentery, can gravitate into either fornix and be palpated on vaginal examination. To this mass the uterus or adnexa may become attached in an effort to prevent the spread of infection or even seal an impending perforation. This intimate association may be detected on vaginal examination and lead one to believe that either primary uterine or adnexal pathology exists. A localized abscess may develop, which may simulate a tuboovarian or pelvic abscess (Case 2). Perforation of the bowel into the free peritoneal cavity at the site of the carcinoma giving rise to a severe peritonitis has occurred several times in our series. Although this may not seem to be of interest to the gynecologist, nevertheless, the onset may suggest a pelvic peritonitis secondary to a tubal infection.

The following 9 cases of carcinoma of the bowel are reported very briefly.

CASE 1.—S. H., 60 years old, has been complaining for the past year of frequency of urination and dysuria associated with pain in the back and left lower quadrant. She had lost 45 pounds in weight. There was nothing else of significance in her history. On vaginal examination there was a mass about the size of an orange, in the left fornix which was also felt just above the left inguinal ligament; this mass was tender and not movable. Tubal infection was suspected. At operation an inoperable carcinoma of the sigmoid was found attached to the lateral pelvic wall. The abdomen was closed.

CASE 2.—D. N., 35 years old, had been operated upon elsewhere, five months before, for a pelvic abscess, which was drained through an abdominal incision. Following the operation she had been well until three weeks prior to admission, when she began to have cramps, marked constipation, and occasional vomiting; she had to resort to frequent enemas which lately were ineffectual. On examination, she was found distended; a small sinus was still present in her previous operative area. It was now believed that she had an intestinal obstruction secondary to a neoplasm in the large bowel, which had previously perforated and gave rise to a pelvic abscess. At operation a carcinoma of the sigmoid was found. A multiple stage Mickulicz operation was done. The pathologic report was a carcinoma. The patient was discharged after eight weeks. The gynecologist who had drained the pelvic abscess evidently overlooked the fact that a carcinoma of the bowel was present.

CASE 3.—P. K., 22 years old, complained of a sharp pain in the left lower quadrant radiating across the abdomen, which began twenty-four hours before admission. There was burning on urination and elevation of temperature. On abdominal examination, diffuse resistance was more pronounced in the left lower quadrant, where there was considerable tenderness. There was a suggestion of an ovoid mass in the left lower quadrant, more easily palpable in the left fornix on vaginal and rectal examination; this mass was quite tender. It was thought that this mass was a twisted ovarian cyst, although a left salpingitis or even an appendicular abscess

could not be definitely excluded. The surgeons concurred in this opinion. The sedimentation time was twenty minutes and gonococcus complement fixation was negative. The urine showed many pus cells and the blood a secondary anemia. At operation a carcinoma of the sigmoid was found with metastasis to the omentum and retroperitoneal lymph glands. The abdomen was drained because of the presence of a moderate amount of seropus; a culture of this turbid fluid was found negative and sections taken from the omentum showed adenocarcinoma. The postoperative course was stormy; she continued to have a septic temperature; she developed a fecal fistula and was discharged six weeks later in a very poor condition.

CASE 4.—J. H., 45 years old, complained of intermittent pains in the left lower quadrant for the past two years, accompanied by gaseous eructations. There was nothing significant in her past history except for loss in weight. On vaginal examination a hard tender mass was felt in the left fornix, which was thought to be an ovarian cyst, possibly malignant. Operation disclosed a large mass in the sigmoid, firmly adherent to a loop of small intestine. The sigmoid could not be mobilized and the abdomen was closed. Later on x-ray study of the large bowel revealed a carcinoma of the pelvic colon. Sixteen days after the first operation, the case was transferred to a surgeon who performed a cecostomy. Three weeks later a Mickulicz operation was done; she did poorly after the operation and notwithstanding supportive measures and a transfusion, she succumbed one week later.

CASE 5.—R. H., 48 years old, had a sense of pressure in the perineum, especially during defecation. During the past five weeks she had several attacks of mild diarrhea, but had not noticed the presence of blood. Her menstrual history was regular up to three months ago; last menstruation occurred five weeks prior to her admission to the hospital. Examination of the lungs revealed chronic fibroid phthisis. On vaginal examination there was felt a hard irregular mass in the cul-de-sac, the size of a hen's egg, slightly tender and somewhat fixed. On rectal examination this mass seemed to be situated in the rectovaginal septum and not encroaching on the rectal lumen. A tentative diagnosis of a tumor in the rectovaginal septum was made. Ovarian malignancy was considered a possibility. The urine and blood were normal; the stool showed the presence of blood. Proctoscopic study disclosed an ulcerating lesion below the rectosigmoid junction, sections of which showed an adenocarcinoma. Two weeks after admission the first stage of an abdominoperineal resection was done. A mass, the size of a fist, was found below the rectosigmoid adherent to the posterior wall of the uterus extending down to the cervix. The patient went into shock after the operation and died twenty hours later.

CASE 6.—E. B., 48 years old, complained of cramps in the lower abdomen for several weeks and constipation for several years; at times she noticed blood in the stool. On examination, the abdomen was moderately distended and not tender. On rectal examination, there was a small hard mass felt through the anterior rectal wall, which did not seem to involve the mucosa. A mass, the size of an egg, was felt in the cul-de-sac attached to the uterus; there was slight bleeding from the os. A tentative diagnosis of carcinoma of the body of the uterus was made although a lesion in the rectum was considered also possible. The urine showed a slight trace of albumin and the blood a moderate anemia. Proctoscopic and roentgen examination disclosed a carcinoma of the sigmoid with almost complete obstruction. A cecostomy was done and three weeks later a Mickulicz resection. The peritoneal fluid showed tumor cells. Two days after the operation, she died of peritonitis.

CASE 7.—E. R., 49 years old, had cramplike pain in the lower abdomen for the past few years, which became aggravated on walking. She has been constipated for many years and in the past year she lost 30 pounds in weight. Six months before she was admitted to the hospital, x-rays of the gastrointestinal tract failed to show any lesion. Her menses were regular until three months ago and since then she had had only one period. The patient appeared cachectic. On vaginal examination, a hard nodular mass was felt in the cul-de-sac; this mass was not tender and seemed fixed to the surrounding structure; the uterus was enlarged. The clinical impression was that she had a carcinoma of the body of the uterus. At op-

eration a carcinoma of the rectosigmoid junction was found adherent to the uterus and pelvis. It was considered inoperable; the abdomen was closed and the patient discharged two weeks later.

CASE 8.—Patient, 38 years of age, complained of abdominal cramps for the past two years, which had no relation to meals. There were no other symptoms. On vaginal examination a hard mass was found attached to the uterus and was thought to be a fibroid. At operation a carcinoma of the rectosigmoid was found adherent to the bladder and uterus. The mass was easily separated, permitting the first stage of a Mickulicz resection. The subsequent steps were completed by the surgical staff and the patient was discharged ten weeks after the first operation. Pathologic study disclosed an adenocarcinoma of the rectosigmoid with lymph gland metastasis.

CASE 9.—M. R., 25 years old, complained of pain in the left lower quadrant for the past month. This pain appeared suddenly and radiated to the back. A slight diarrhea and frequency of urination accompanied the onset of this pain. Examination of the abdomen revealed a palpable sigmoid colon. On vaginal examination the uterus felt normal. A mass was felt in the left fornix, the size of a hen's egg; it was fixed and slightly tender. This mass could also be felt on rectal palpation although the rectal mucosa seemed free. The opinion was that this mass was inflammatory, although carcinoma of the ovary was also considered likely. A junior member of the gynecologic staff advised study of the colon and rectum because he could not exclude a lesion of the bowel. At operation, a rectosigmoid carcinoma was found. A surgeon was immediately available to perform the first stage of an abdominoperineal resection. A diagnosis of carcinoma was confirmed by the pathologist. Eleven days later the second stage was completed and the patient died of shock several hours later.

These cases are reported to illustrate how a lesion such as a carcinoma of the bowel can simulate a gynecologic disorder and justify to a certain extent the clinical errors committed not only by the gynecologist but the surgeon as well. We do feel, however, that a very careful evaluation of symptoms and findings should help one to avoid such pitfalls in diagnosis. In the many cases that come to the gynecologist with some lesion of the generative organs, the task of recognizing the pathologic nature of the disorder is comparatively simple because of the definite characteristic features presented by a fibroid, ovarian cyst or tubal condition; usually the clinical diagnosis is confirmed at operation. It is always well to suspect a neoplasm in the colon when a mass is found on vaginal examination which does not conform to the characteristics of either one of the above lesions, particularly if there are symptoms referable to the large bowel. We do not advocate the indiscriminate use of the x-ray or the proctoscope in those cases where a gynecologic disorder is clearly established; nevertheless, in the more obscure cases with an undefined pelvic mass the application of these necessary diagnostic procedures will not only help clarify the origin of a pelvic mass but also reduce the incidence of error.

In Case 9, there were symptoms referable to the large bowel and barium enema was suggested to determine if the mass had any connection with the colon. In Cases 5 and 6, a gynecologic lesion was believed to exist but because of the unusual features of the palpable mass, proctologic examination was made and disclosed the mass to be a carcinoma in the bowel.

In routine practice, when the gynecologist mistakes a fibroid for an ovarian cyst or hydrosalpinx, it is of no great importance. The patient's postoperative course is not affected by this clinical error. When, however, he finds an unsuspected carcinoma of the colon, the consequences of such error may have serious sequelae. The preparation for the routine gynecologic operation is not very important, whereas the prognosis in patients to be operated upon for carcinoma of the large bowel depends very much on proper preoperative preparation of the patient. Any attempt at radical removal of the growth even by a competent gynecologist or surgeon when the patient is not properly prepared for it is to be avoided.

The problem arises as to the mode of procedure in the event that the lesion is unexpectedly found at operation. To the gynecologist who is an experienced abdominal surgeon, there will be no difficulty in proceeding along accepted surgical lines. If his surgical experience is limited to the reproductive organs, he will undoubtedly content himself with closing the abdomen and transferring the patient to a surgeon or even feel that the case is inoperable. We strongly recommend, under such conditions, a preliminary cecostomy which is easily performed and might even shorten the surgical period. The major operation can then be deferred to the surgeon. The diversion of the fecal stream is particularly advantageous when either a partial or complete obstruction is present. Cecostomy decompresses the bowel and more thoroughly prepares the patient for the subsequent surgical procedures. Not infrequently a carcinoma of the bowel, because of the associated ulceration and infection, will give rise to a mass largely consisting of inflammatory reaction. This might give the erroneous impression at the time of exploration that an inoperable lesion exists, as was the case in Patients 1 and 7. It is surprising how this inflammatory reaction will subside and the mass diminish greatly in size after the fecal current is diverted by means of a cecostomy. What was first considered to be an apparently inoperable growth becomes more readily resectable. If an abscess is present as in Case 2, simple drainage should suffice for the time being, because any attempt at more radical surgery at this time would jeopardize the patient's chance for recovery.

It is needless to state that the mere invasion of the uterus or adnexa or their attachment to the mass does not preclude a radical extirpation of the bowel. The removal of the uterus with its adnexa along with the colon neoplasm is not a difficult procedure and should not discourage the surgeon.

SUMMARY

Several cases of carcinoma of the large bowel are reported which because of their clinical features were erroneously diagnosed as suffering from a gynecologic disorder.

We believe that a more careful evaluation of the clinical findings and history, and the application of the proper diagnostic procedures,

in some of the patients who present an obscure pelvic mass, will undoubtedly help to eliminate such errors.

In cases of such mistaken diagnosis, the gynecologist should bear in mind that a cecostomy is a preparatory and most valuable step in the surgical management of the cases.

If at operation a pelvic abscess is found whose origin seems uncertain, one should determine subsequent to surgical drainage, if there is any possible connection to a growth in the large bowel.

1882 GRAND CONCOURSE

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PITOCIN IN THE THIRD STAGE OF LABOR

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THE effect of pitocin on the duration of the third stage of labor was observed in 630 patients. The blood loss incident to the separation and delivery of the placenta was determined in each case. The observations included blood pressure changes and systemic manifestations following the intravenous and intramuscular injection of pitocin. The undesirable pressor effect of pitressin and pituitrin as well as the danger of an allergic reaction was avoided by the use of pitocin.

METHOD

An oxytocic was administered routinely at the beginning of the third stage to a series of patients with normal and abnormal pregnancies. This series included operative as well as spontaneous deliveries. Pitocin was administered intravenously, except in a few cases in which difficulty was experienced in passing the needle into the vein, then it was given intramuscularly. In a few instances pituitrin was given intramuscularly, but never intravenously. Ergotrate was also given intramuscularly in a few cases. The blood pressure was taken routinely during the first and second stages of labor and repeated three minutes after the injection. The patient's arm was prepared during the second stage for the intravenous injection to avoid any delay at the onset of the third stage. After aspirating 2 to 3 c.c. of blood to dilute the pitocin, the mixture was injected slowly over a period of one minute. During the third stage the blood was collected in a basin held against the perineum. Expulsion of the placenta from the lower uterine segment and the upper part of the vagina was done routinely as soon as the separation of the placenta was completed. In each case the amount of blood loss on drapes and sponges was estimated. No attempt was made to exclude blood loss from episiotomy wounds or cervical and vaginal lacerations. The collected blood was not infrequently contaminated with amniotic fluid. The hemoglobin was determined just before delivery and again on the tenth day of the puerperium.

In the present series of 630 patients, 505 received 0.5 c.c. of pitocin intravenously immediately following the delivery of the baby, and 125 patients received 0.5 to 1.0 c.c. of pituitrin or pitocin intramuscularly. In each instance the total blood loss was recorded, which equals the measured blood collected in the placenta basin plus the estimated blood loss on drapes and sponges.

RESULTS

The patients, who received intravenous pitocin, had an average blood loss of 171.0 c.c., a measured blood loss of 66.5 c.c., and an estimated blood loss of 104.5 c.c. In the comparison those patients, who received an oxytocic intramuscularly, had an average total blood loss of 203.9 c.c., a measured blood loss of 83.3 c.c., and an estimated blood loss of 120.6 c.c. Of those patients who received intravenous pitocin, 50.0 per cent had a total blood loss of less than 150 c.c., and 89.1 per cent had a measured blood loss of less than 150.0 c.c. Of those who received an oxytocic intramuscularly, only 28.0 per cent had a total blood loss of less than 150.0 c.c., and 72 per cent had a measured blood loss of less than this amount. The foregoing figures indicate a definite advantage in the use of intravenous pitocin over the intramuscular injection. Tables I and II and the curves in Fig. 1 show that among those patients who lost less than 150 c.c. of blood, there was a higher percentage of those who received intravenous pitocin than there was of those who received an oxytocic intramuscularly.

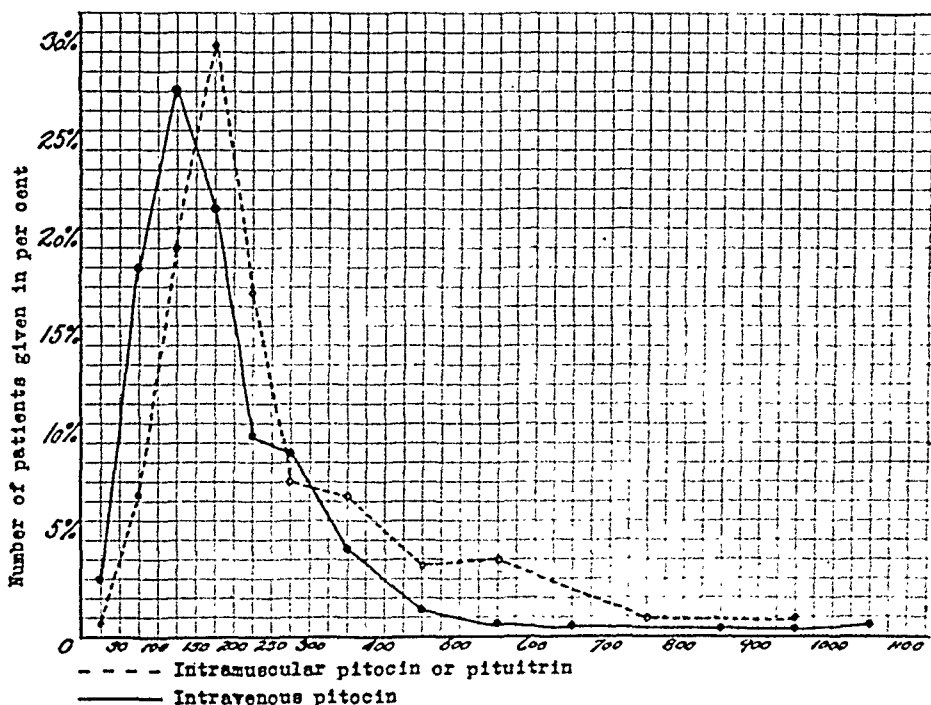


Fig. 1.—The blood loss is shown in cubic centimeters. The number of patients in each group is expressed in percentage. The curves show that of the patients who received intravenous pitocin a larger percentage lost less than 150 c.c. of blood than was the case with those patients who received intramuscular pitocin or pituitrin.

The average duration of the third stage was 5.4 minutes with the intravenous pitocin and 6.5 minutes with the intramuscular oxytocic. In the group of patients receiving intravenous pitocin, the delivery of the placenta was frequently completed before all the pitocin had been injected into the arm vein. Retention of the placenta requiring manual removal occurred only twice in the entire group of patients, and in both the cervix was found to be open.

On the tenth day of the puerperium the average hemoglobin reading of those patients who received intravenous pitocin was 4.3 per cent higher than that of the patients who received intramuscular pitocin or pituitrin.

DISCUSSION

Pitocin has been selected as the oxytocic in this study for the following reasons: (a) it produces no appreciable change in blood pressure, except when traces of the pressor principle are present; (b) this oxytocic is

TABLE I. DATA OF PATIENTS GIVEN INTRAVENOUS PITOCIN

The Distribution of Blood Loss Among 505 Patients Who Received Intravenous Pitocin at the Beginning of the Third Stage of Labor

BLOOD LOSS C.C.	NO. PATIENTS TOTAL BLOOD LOSS	NO. PATIENTS MEASURED BLOOD LOSS	NO. PATIENTS ESTIMATED BLOOD LOSS	PER CENT OF PATIENTS WITH TOTAL BLOOD LOSS
1000	2	1		0.4
900-1000	1			0.2
800- 900	1			0.2
700- 800				
600- 700	3		1	0.6
500- 600	3	3	3	0.6
400- 500	6	1		1.2
300- 400	24	4	8	4.5
250- 300	48	3	7	9.6
200- 250	54	10	31	10.4
150- 200	110	33	53	22.0
100- 150	143	97	145	28.0
50- 100	95	169	200	19.0
0- 50	15	184	57	3.0

TABLE II. DATA OF PATIENTS GIVEN INTRAMUSCULAR PITOCIN OR PITUITRIN

The Distribution of Blood Loss Among 125 Patients Who Received Intramuscular Pitocin or Pituitrin at the Beginning of the Third Stage of Labor

BLOOD LOSS C.C.	NO. PATIENTS TOTAL BLOOD LOSS	NO. PATIENTS MEASURED BLOOD LOSS	NO. PATIENTS ESTIMATED BLOOD LOSS	PER CENT OF PATIENTS WITH TOTAL BLOOD LOSS
1000				
900-1000	1			0.8
800- 900				
700- 800	1			0.8
600- 700				
500- 600	5	3	1	4.0
400- 500	4		2	3.6
300- 400	9	1	6	7.2
250- 300	10		5	8.0
200- 250	22	14	6	17.6
150- 200	38	17	10	30.4
100- 150	25	21	35	20.0
50- 100	9	42	52	7.2
0- 50	1	27	8	0.8

a nonprotein which does not subject the patient to the dangers of an allergic reaction; (c) the use of intravenous pitocin in unanesthetized patients indicated that this oxytocic does not produce any deleterious effect; (d) its use is not contraindicated in patients with toxemias of pregnancy, chronic nephritis, or arterial hypertension; (e) it produces a contraction of the uterus within one minute following the intravenous administration; (f) there is evidence that this principle will yield more satisfactory and uniform oxytocic results when administered by itself, than when mixed with the pressor hormone (Kamm¹).

While pituitrin is commonly used in repeated doses to control hemorrhage after the delivery of the placenta, the indiscriminate use of this hormone is to be deprecated because of the constrictor effect on the

peripheral circulation and the depressor effect on the heart. For these reasons pituitrin is contraindicated in arterial hypertension, chronic myocarditis, and the toxemias of pregnancy.

Pastore² has reported one fatality, which may have been due to the intravenous use of pituitrin. Simon³ has reported a case with specific hypersensitiveness to pituitary extract, in which there was no personal or family history of allergy and with negative tests to the common allergens. In this patient pitressin gave a positive test and pitocin gave a negative allergic reaction. Schoekaert⁴ reported a woman with a normal obstetric course, in whom eclamptic-form convulsions developed following the injection of pituitrin, and concluded that this manifestation was due to the vasopressor component. Dieckmann and others⁵ have indicated that the use of pituitrin is contraindicated in pre-eclamptic patients, whereas pitocin does not produce any undesirable effects in the toxemic patient.

Shock was noted in only one case in the series of 630 patients. This occurred in a patient with a toxemia, who had received intravenous pitocin. Signs of circulatory collapse did not develop until one hour after delivery.

This patient had previously lost six premature babies. She was admitted to the hospital at the end of the seventh month of gestation, because of albuminuria and a blood pressure of 180/136. She was under observation for a period of four weeks and then labor was induced by the insertion of a bougie. The labor was of six hours' duration and the delivery was spontaneous, with a blood loss of 415 c.c. Her hemoglobin reading prior to delivery was 62 per cent. Following transfusion and supportive treatment the patient made a satisfactory recovery, although she continued to have hypertension and albuminuria. In order to determine whether or not the intravenous pitocin was a factor in producing the state of shock, she was subsequently tested with intravenous pitocin. As a result of this test there was no appreciable change in blood pressure, and no signs or symptoms of any systemic disturbance. It was concluded that the shock was the result of blood loss, which was relatively large for a debilitated and toxic patient, whose hemoglobin prior to delivery was relatively low.

SUMMARY AND CONCLUSIONS

1. The intravenous and intramuscular administration of pitocin produces no undesirable systemic effects.
2. The use of pitocin is not contraindicated in the toxemias of pregnancy.
3. Intravenous pitocin at the beginning of the third stage of labor induces a prompt and uniform contraction of the uterus which hastens the separation and expulsion of the placenta without evidence of trauma to the uterus or laceration of the placenta and membranes.
4. There is no increase in the incidence of retained placenta following the use of pitocin in the third stage.
5. The average total blood loss in 505 patients who received intravenous pitocin at the onset of the third stage was 171 c.c. and the average measured blood loss was 66.5 c.c.
6. The average total blood loss in 125 patients who received intramuscular pitocin at the onset of the third stage was 203.9 c.c. and the average measured blood loss was 83.3 c.c.

7. With the intravenous use of pitocin the average duration of the third stage was 5.4 minutes and with the intramuscular administration 6.5 minutes.

8. The intravenous use of pitocin in the third stage is preferred to the intramuscular injection because the oxytocic reaction occurs with greater rapidity.

9. The duration of the oxytocic action of pitocin is shorter than that of ergotrate.

I wish to thank Dr. J. P. Pratt for the opportunity of carrying out this study and for his helpful suggestions in the preparation of this paper.

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VAGINECTOMY*

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ONE of the major problems in operative gynecology is the selection of the operation best suited for the repair of hernias through the birth canal. The most important considerations are: first, the extent of the hernia; second, the age of the patient; third, the social state of the patient; and fourth, the patient's wish in the matter.

In cases of postoperative vaginal hernia and in cases of procidentia in which the patients are elderly women, especially if the procidentia is associated with a large cystocele or an enterocele,⁸ it is often a difficult problem to replace the prolapsed organs and reconstruct a satisfactory vaginal canal. In many cases, if the patients will give their consent, the most satisfactory operation is one that will more or less close the vagina. Operations of this type are listed under the titles of "colpocleisis," "vaginectomy" and "colpectomy."

Vaginectomy necessarily results in a complete cessation of sexual relations and this should be explained to the patient and her husband. Most of the patients who were subjected to vaginectomy at The Mayo Clinic were past the menopause (the average age is 58.5 years) and had had multiple operations. The exposure and irritation of the vaginal mucous membrane had caused an unnatural dryness and thickening which usually had caused the cessation of sexual relations before the patients sought medical advice. The operation gives uniformly good results; it eliminates the bearing-down feeling, the discomfort, the urinary frequency, and the difficulty in emptying the

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rectum, which are cardinal symptoms of gynecologic hernia. The prospect of cure is all the patients desire.

Partial and complete vaginectomy has been done in Europe since 1877, when Le Fort described his operation under the title of partial vaginectomy. The first mention of the procedure in the American literature was by Edebohls, who called his operation panhysterokolpectomy. In the first case in which he performed the operation the patient had had many operations without relief. He reported 4 cases in which the uterus was removed along with the vagina; the results were uniformly good. Gallant reported a case in which the operation was performed. Demarest reported 10 cases in which the operation produced satisfactory results and described a technic of operation. Dujarier and Larget reported 15 cases in which the results of the operation were excellent. Simon reported a total of 92 cases, 2 of his own, in which a follow-up of 59 patients revealed that symptoms recurred in only one case. Baer and Reis in 1928 reported favorably on the results of the Le Fort operation in 14 cases. Rubovits and Litt in 1935 reported favorable results in 19 patients in whom a Le Fort operation was performed and in 1 patient in whom a total vaginectomy was performed. In 1935, Phaneuf wrote a paper on colpectomy in the treatment of uterine and vaginal prolapse.

It is surprising that so little has been written in this country on this important surgical procedure, as we are satisfied that it is used in at least a modified degree much more frequently than a perusal of the literature would lead us to believe. We are satisfied that in the majority of cases in which it is not possible to reconstruct a vaginal canal of approximately normal length, the surgeon is justified in closing the vagina if the patient will give her consent, especially if the patient is an elderly woman.

In a case in which closure of the vagina seems advisable and the uterus has not been removed at a previous operation, the surgeon has a choice of two operations: a complete colpectomy and a partial colpectomy. If a complete vaginectomy is contemplated and is considered the better operation, it is absolutely necessary to remove the uterus at the same time that the vagina is occluded. Even after the menopause, there is a certain amount of drainage from the endometrium and endocervix, which must be provided for if the uterus is not removed. Fortunately, a vaginal hysterectomy is very easy in this type of case as there is always marked prolapse.

In case a partial vaginectomy is advised, it will not be necessary to remove the uterus, but provision for uterine drainage must be provided. This is well cared for by the Le Fort operation, which obliterates the central portion of the vagina almost to the cervix and leaves a narrow open space on each side. There probably is a useful field for this operation as even some elderly patients will object to the removal of the uterus.

Besides these two types of vaginectomy, surgeons all know that following many vaginal hysterectomies⁷ which are performed for marked

degrees of prolapse associated with large cystocele and high rectocele the upper part of the vagina is occluded in order to give strength to the closure. In many cases this shortening is just as much an inconvenience to the patient as is a total closure of the vagina and it is less likely to cure a gynecologic hernia than is the latter procedure.

TECHNIC OF TOTAL VAGINECTOMY

The technic of the operation varies considerably in the individual case, depending on what structures are available to close the opening. If the uterus is present, it is essential to remove it. After approximating the broad ligaments in the median line and firmly fixing them well up under the pubic arch, they can be sutured posteriorly to the levator ani muscles which are thoroughly freed and sutured in the

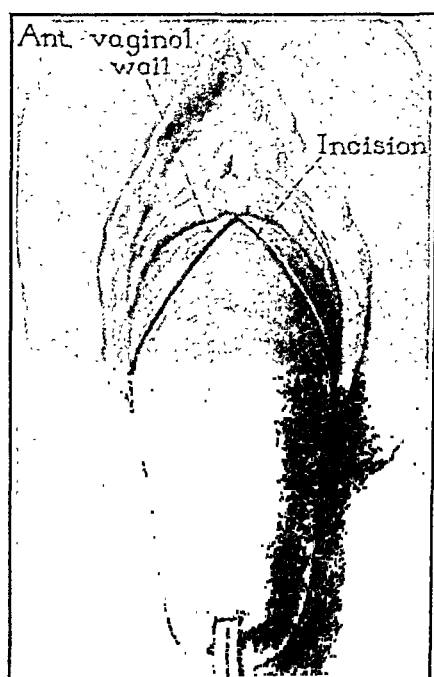


Fig. 1.

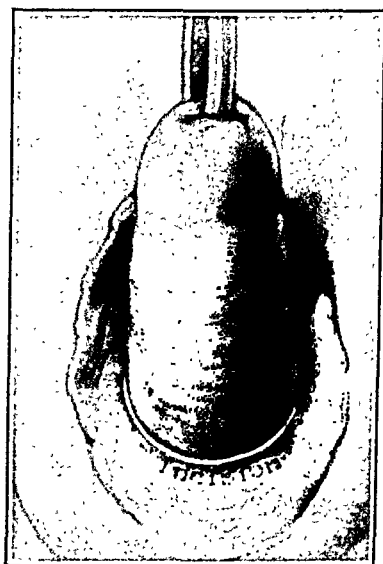


Fig. 2.

Fig. 1.—“V” shaped incision in anterior vaginal mucosa.

Fig. 2.—Circular incision of posterior vaginal mucosa at the level of the hymenal ring.

median line as they are in an ordinary perineorrhaphy. In this manner a strong pelvic floor is reconstructed and the closure of the rest of the vagina is easily accomplished, after removal of all mucous membrane, by interrupted transverse sutures, some of which are silk-worm gut and are left in place for twelve to fourteen days. It is advisable to provide for drainage by inserting a small tube. If an enterocele is present, the peritoneal sac should be removed before commencing the closure.

If the uterus has been removed at a previous operation, it is often not necessary to open the peritoneal cavity. The mucosa is removed as advised previously. The levator ani muscles are approximated as in a perineorrhaphy and the pubovesical fascia and urogenital septum

are approximated in the median line and utilized to close the anterior part of the hernial opening and support the bladder. The denuded vaginal walls below this newly constructed pelvic diaphragm are approximated by interrupted transverse sutures, thus making a firm closure of what was formerly the vaginal canal (Figs. 1, 2, 3, 4, and 5).

The technic of the Le Fort partial vaginectomy is as follows: A strip of mucous membrane about 2 cm. wide is denuded from the anterior wall of the vagina from a point about 1 cm. below the

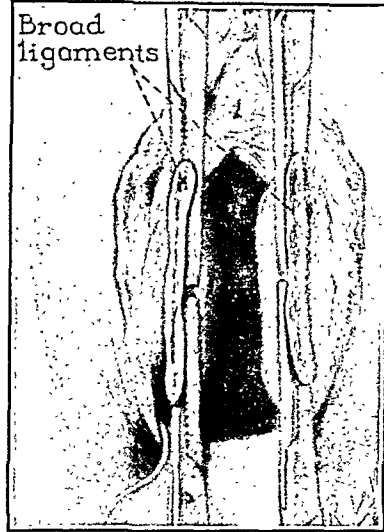


Fig. 3.—Approximation of broad ligaments when a vaginal hysterectomy is also done.

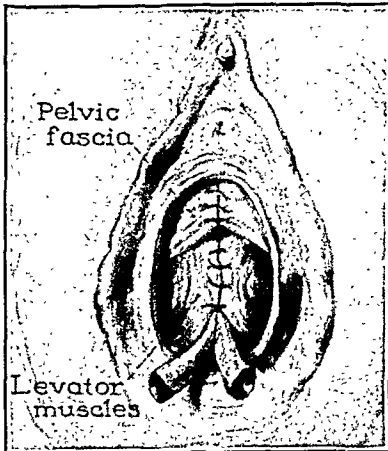


Fig. 4.

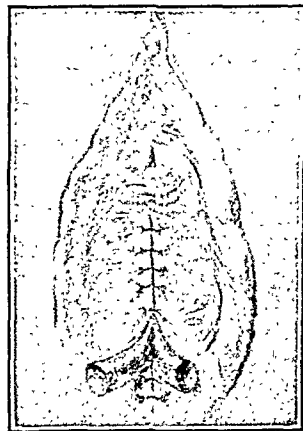


Fig. 5.

Fig. 4.—Approximation of levator muscles and pelvic fascia up to the pubic arch.
Fig. 5.—Approximation of mucosa; complete absence of vaginal canal.

urethral orifice to within 2 cm. of the cervical os. A similar area is denuded on the posterior vaginal wall. These two raw surfaces are accurately sutured together by commencing at the cervix and working upward and invaginating the prolapsed vagina, thus forcing the uterus upward. When the operation is completed there will be a mucous-lined tract from the cervix down each side of what formerly was the vagina. In all cases a high perineorrhaphy should be a final step in the operation (Fig. 6).

In the series of 23 cases in which complete vaginectomy was performed at The Mayo Clinic from 1910 to 1937, the oldest patient was 69 years of age and the youngest was 44 years of age; the average age of the patients was 58.5 years. In 7 patients a hysterectomy and vaginectomy were performed at the same time, while in 16 patients a vaginectomy only was done, as the uterus had been removed previously. Nineteen patients (82.6 per cent) were traced and found to be cured; 3 had some irritability of the bladder. No patient had a recurrence of the prolapse or hernia. Previous to operation this

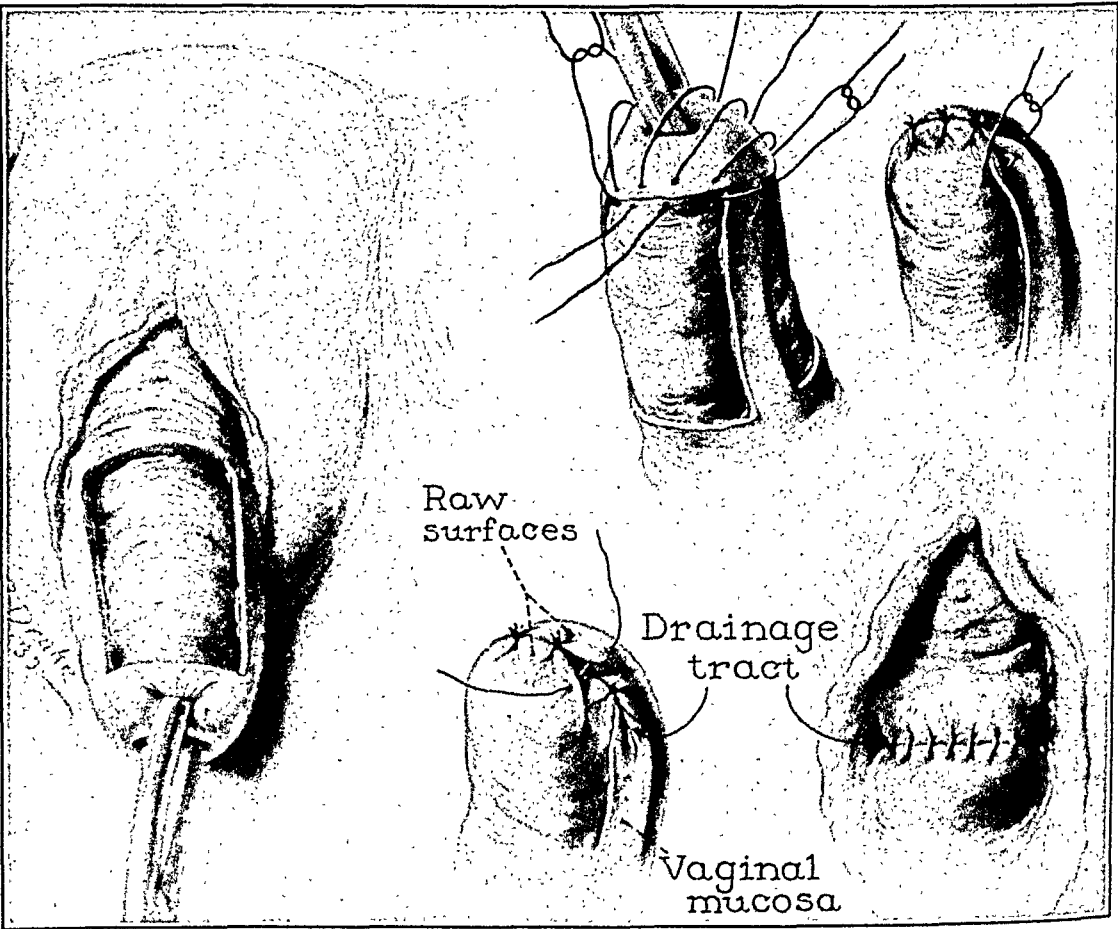


Fig. 6.—Technic of Le Fort's operation, showing partial vaginectomy.

group of patients had had 94 children, an average of more than 4 children per patient. One patient was unmarried and had not had any children; she had virginal prolapse. Seventeen patients had had previous operations for this condition, and 2 of them had been operated on four times. One patient died of pulmonary embolism on the thirtieth postoperative day. It just happened in this series there were no cases in which the Le Fort partial vaginectomy was performed. There is no doubt that it is a satisfactory operation in most cases but we believe the complete operation to be preferable. The removal of the uterus at the same time as the closure of the vagina adds very little to the operation.

CONCLUSIONS

1. In gynecologic hernias, the selection of the operation best suited to the individual case is important.
2. In the more difficult hernias which affect elderly patients some type of vaginectomy is justifiable.
3. Comparatively few cases of either partial or complete vaginectomy are recorded in American literature.
4. There is no doubt in our minds that a partial vaginectomy with removal of more or less of the upper part of the vagina is a rather common practice associated with a vaginal hysterectomy but that it is not reported.
5. The Le Fort operation with preservation of the uterus is a safe and satisfactory operation.
6. Complete vaginectomy with removal of the uterus is the operation of choice in many cases in which elderly women have procidentia of high degree and also is often indicated in cases in which vaginal hernia follows a previous hysterectomy.

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THE BILIRUBIN LIVER FUNCTION TEST IN THE TOXEMIAS OF PREGNANCY

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TWENTY cases of abnormal pregnancy in which hepatic function tests have been made at some period during the disorder is the content of this report. In an attempt to gain liver function information relative to the toxemias, the cases are essentially restricted to eclampsia, preeclamptic toxemia, nephritic toxemia, vomiting of pregnancy, and premature separation of the placenta.

Functional demands of gestation not infrequently embarrass not only the kidney but also the liver during the last trimester.⁵ The ill-defined delimiting zone between normal and abnormal suggests the importance of individual tests in estimating the degree of latent or definite hepatopathy associated with abnormalities of the gravid state.

Observers^{4, 5} who have had experience with several tests for hepatic function agree that the bilirubin retention method is the most sensitive

single test adaptable to clinical use. Utilization of a physiologic substance in a function similar to that continually demanded of the organ seems reasonable. This material is neither removed by the Kupffer cells nor excreted by the kidney.

That there is a notable limitation by the estimation of but a single function in an organ of manifold rôles is recognized.

Since von Bergmann³ and also Eilbott² employed the excretion of intravenously injected bilirubin to ascertain the relative degree of hepatic function, there has been a satisfactory procedure for this purpose. Modifications by Harrop⁴ and subsequently by Soffer⁵ have been adopted. These investigators consider retention in excess of 5 per cent after four hours to be abnormal.

Soffer⁵ and subsequently Sullivan⁶ have shown evidence of a tendency to decreased excretion rate for bilirubin during the last half of gestation as compared with the initial half. The former observed an average of 1.6 per cent for the first half and 7.1 per cent during the second half of pregnancy. The latter attempted to differentiate the toxemias into predominantly nephritic and hepatic groups. An average retention of 19 per cent ante partum and 5 per cent post partum was reported.

METHOD

A resting blood specimen is drawn from an antecubital vein and immediately 1 mg. of bilirubin (Eastman Kodak Co.) per kilogram of body weight dissolved in 15 centiliters of 0.1 molar sodium carbonate is injected through the original needle. Five minutes later a specimen is drawn from the contralateral arm. A high bilirubin content will be observed in this second specimen; whereas the initial specimen contains lipochromes and possibly carotin. Upon subtracting the initial from the second value the introduced quantity or 100 per cent is obtained. After four hours a third sample is drawn which, after subtracting the initial value, is compared with the second and the result expressed in percentage of the quantity introduced. Using the colorimetric method of Ernst and Forster,¹ the bilirubin concentration is determined on the centrifugalized acetone precipitated plasma.

RESULTS

Showing an average bilirubin retention of 11.8 per cent four hours after injection this series of heterogeneous toxemias presents notably decreased pigment elimination as compared with the average of the normal pregnant series reported by Soffer.⁵ Four of the group presented had eliminated all bilirubin administered within the test period. These included one individual classified as an example of essential hypertension, two patients with nephritis or nephritic toxemias and one instance of preeclamptic toxemia. Each of these four had some albuminuria and evidence of hypertension.

Noteworthy is the intrapartum test on a patient with premature separation of the placenta in which half of the dye was retained for four hours. This individual gave clinical evidence of marked toxemia and subsequently was delivered of a stillborn fetus after introduction of a Voorhees' bag.

TABLE I. BILIRUBIN RETENTION FOLLOWING INTRAVENOUS ADMINISTRATION

PA- TIENT	AGE	PAR- ITY	WEIGHT KG.	E. D. C.	DELIVERY DATE	BILIRUBIN TEST DATE	BILIRUBIN RE- TENTION PER CENT	BLOOD PRESSURE	ICTERIC INDEX	FIBRIN- OGEN	URINARY ALBU- MIN	REMARKS
<i>Icterus</i>												
H. L.	33	1	79.4	7/ 1/36	5/25/36	5/23/36	8.4%	190/120	10	0.60	4+	Prem. 1 mo. Labor induced 4 da. after convulsions.
H. B.	34	13	96.8	6/10/36	4/26/36	4/24/36	9.5%	210/100	8	0.46	4+	Prem. 2 mo. Convulsions on admis- sion.
*M. D.	17	0	53.6	8/28/35	7/29/35	8/ 5/35	11.4%	150/110	3	0.39	1+	Post partum (18 hr.) recurrent eclampsia.
G. N.	31	0	58.7	4/29/36	4/ 7/36	4/ 8/36	7.6%	160/ 90	10	0.20	4+	Intrapartum eclampsia.
<i>Vomiting of Pregnancy</i>												
H. M.	25	1	64.8	11/ 6/36	5/ 6/36	5/ 5/36	37.4%	138/100	24	0.47	0	Ther. abort. Died 5/11/36. Icteric index 8 on 5/11/36.
M. S.	30	5	84.6	11/19/36	11/29/36	5/ 8/36	9.2%	120/ 78	12	---	trace	Tox. vomiting, acetone +, diacetic 4.
R. T.	22	0	59.2	6/27/35	6/21/35	11/ 9/34	25.9%	120/ 80	10	0.55	trace	Acet. 4, Diacet. 4.
<i>Pre-eclamptic Toxemia</i>												
L. M.	35	1	75.4	8/20/35	8/21/35	8/18/35	4.0%	140/100	6	---	3+	Induction of labor 8/21/35.
E. P.	19	0	71.0	1/23/35	1/11/35	1/11/35	0	132/ 90	8	---	trace	-----
J. G.	34	7	71.5	3/27/36	-----	3/10/36	7.0%	210/100	8	0.27	4+	Died in labor, 4/11/36; ? pre. sep. pla.
J. G.	19	0	77.0	3/18/36	2/11/36	1/30/36	14.9%	145/ 84	--	---	2+	-----
<i>Premature Separation of Placenta</i>												
S. K.	25	0	45.8	9/17/35	8/21/35	8/20/35	51.0%	140/100	12	---	4+	Vorhees' bag induction of labor.
<i>Pregnancy Abnormal With Nephritis</i>												
A. K.	27	1	90.0	8/17/35	8/15/35	7/23/35	0	190/130	--	0.45	2+	-----
K. P.	32	0	68.0	8/ 3/35	8/ 8/35	7/11/35	10.9%	182/100	--	---	1+	Urine cult. anaerobic strep. mac. fo- tus. Macerated fetus
M. E.	42	7	59.4	5/17/36	4/11/36	3/ 6/36	0	240/128	6	0.52	4+	Premature delivery.
M. G.	34	1	44.6	3/10/36	3/11/36	3/ 3/36	12.1%	122/ 84	6	---	0	Cesarean section for sterilization.
P. M.	39	3	100.0	1/21/36	1/18/36	1/15/36	3.2%	160/ 90	--	0.31	trace	Hypoehr. anemia, sec. hyperten.
N. M.	31	2	58.3	6/19/35	11/ 9/34	9/12/34	15.4%	132/ 82	--	0.23	1+	Supravag. hysterectomy of gravid uterus.
<i>Missed Abortion</i>												
L. W.	28		57.0	10/20/35	7/ 4/36	6/29/36	7.9%	130/ 80	6	0.10	0	Spon. abortion following transfusion reaction.
<i>Essential Hypertension</i>												
L. G.	34	3	74.0	4/27/35	3/23/35	3/18/35	0	165/110	6	0.44	trace	Induction of labor, prem. delivery.

*Fibrinogen 0.63 on 8/2/35.

The vomiting of pregnancy group averaged a 24 per cent retention of the dye in the allotted time. These tests were carried out during the first trimester of gestation. Increases in the icteric indices were noted in all of these cases. Where tests for acetone bodies were done, positive findings were present.

Pre-eclamptic toxemia in this series shows an average retention of 6.5 per cent during the latter weeks of pregnancy. Albuminuria and a tendency of hypertension were observed in the last few weeks of pregnancy in each instance. The previous history had been negative for disturbances during late pregnancy and the abnormal findings were restored to normal limits upon discharge. Transient edema of the hands and face was occasionally recorded but no edema of the fundus oculi was noted. Renal function as determined by urea clearance and Addis cast counts were not remarkably abnormal in this group.

Eclampsia as reflected in bilirubin elimination tests carried out at various times near or following the date of delivery gives an average retention of 9.2 per cent which is about twice the normal limit. Although normal pregnancy may present an increased bilirubin elimination time,⁵ in this group there were no normal cases. A definite but slight tendency to diminished liver function is indicated in eclampsia. Blood pressure was consistently elevated, often to a marked degree. Furthermore notable albuminuria was present in every instance. The tendency to increased icteric index values was not marked. Fibrinogen determinations show an average of 0.41 mg. per cent and a correlation with the dye test is not established.

Chronic nephritic toxemia as manifested in bilirubin function presents an average retention of 6.9 per cent which is somewhat more than that established for normal pregnancy, but individual variations ranged from 0 to 15.4 per cent. Well recognized are the difficulties in diagnosis in this group. Frequently proper classification is definitely established only after careful studies many months post partum. Although the relatively early onset, history of previous episodes during an antecedent pregnancy, and chronic course suggested a nephritic basis, in some instances at least there was a significant retention of injected bilirubin. Where examinations of the fundi were recorded, the only abnormalities were vascular. The urea clearance and Addis cast count procedures gave values which were usually diminished. The albuminuria was variable quantitatively. No edema of significance was reported. Hypertension was usually marked, although two instances of consistently moderate pressure readings are noted.

As presented in the table, an instance of missed abortion was tested six days prior to expulsion of the fetus. Slight retention (7.9 per cent) was observed with no increase in icteric index or primary evidence of toxemia.

Remarkable is the striking retention amounting to 51 per cent found in an individual with outspoken clinical signs of premature separation of the placenta. There was hypertension and marked albuminuria together with an elevated icteric index of twice the upper normal

limit. With the sudden onset, this instance of acute toxemia displayed within a few hours pronounced symptoms of a critical disturbance only to subside rapidly subsequent to termination of the induced labor.

A single instance of decided hypertension presented no hepatic dysfunction, nor were the associated tests abnormal.

DISCUSSION

The icteric index may be elevated in liver dysfunction but in disturbances of some days' duration the tendency is toward subsidence even though the bilirubin elimination remains delayed. Apparently it varies from case to case but properly interpreted may be a gross guide to the bilirubin excretion capacity of the liver. In the presence of persistent clinical icterus there is ordinarily no indication for a bilirubin excretion test.

Fibrinogen values are frequently low in experimental hepatic damage in dogs, but no correlation was established with bilirubin excretion values in this series.

Nephritis during pregnancy would not be expected to show altered bilirubin excretion, especially since the dye is not eliminated by the kidney in man. However, it is possible that the pregnancy liver of earlier writers is disturbed to a variable extent during the altered metabolism of the final trimester in instances of chronic nephritis. It seems unnecessary to postulate the coexistence of two entities.

As an alternate possibility the several instances of increased retention may eventually show normal kidney findings and future normal pregnancies. This would suggest a reclassification as pre-eclamptic toxemias.

SUMMARY

Toxemias of pregnancy cannot be nosologically arranged on the basis of the bilirubin hepatic function test. However, this procedure is probably our most adaptable measure of the labile and manifold functioning liver. As such it may be of value together with renal function tests to aid in establishing a delimiting zone between the nephritic and pre-eclamptic toxemias.

CONCLUSIONS

Hepatic function tests by the bilirubin elimination method have been studied in twenty cases of abnormal pregnancy in which the average retention was 11.8 per cent.

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THE POTENTIAL BISEXUAL CHARACTER OF THE OVARY*

A PRELIMINARY REPORT

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IN PREPARATION for the development of the genital system each embryo, whether it be "determined" as male or female, provides itself with materials from which may develop the organs of either sex, that is, paired gonads, two mesonephroi (Wolffian bodies) with their ducts, and the paired Müllerian ducts. To produce male generative organs the gonads become progressively developed into testes, the mesonephric tubules become the efferent ductules of the epididymides, and the mesonephric ducts transform into the vasa deferentia. The Müllerian ducts degenerate wholly or, in part, remain as vestigial structures. Reciprocally, in the event of female development, the gonads become markedly modified to produce ovaries, the Müllerian ducts remain, while the entire mesonephric apparatus partially degenerates and persists vestigially.

For a better understanding of the subsequent observations a brief detailed description of the development and differentiation of the gonad into the ovary or testis is necessary. As a result of cellular proliferation of the mesothelium covering the ventromedial borders of the urogenital folds in the embryo, paired longitudinal prominences, the genital folds, are produced. Continued development and expansion of the genital folds produce oblong gonads suspended from the ventromedial sides of the mesonephroi. Each gonad is composed of: (1) a mesothelial covering (germinal epithelium) which has formed (2) an inner epithelial mass and (3) rete cords. In the differentiation of a testis the inner mass becomes separated from the germinal epithelium by the formation of an intervening connective tissue tunica albuginea. The inner mass becomes cordlike due to the appearance of septa and later becomes the testis tubules. The rete mass or cords transform into the rete testis, connecting distally with the testis cords and proximally with the cranial group of mesonephric tubules. Germinal cells and Sertoli ("nurse") cells develop in and from the epithelial testis cords. Male interstitial cells originate from the surrounding connective tissue cells (Wilson) or from the germ cells which are not included in the tubules (Simkins). It is probable that in either case the production of interstitial cells is dependent upon influences exerted by the medullary cords (testis tubules).

If an ovary is to be differentiated, the tunica albuginea does not form and therefore the germinal epithelium is permitted to continue its proliferation of cells upon the central epithelial mass, thus producing an outer cortex (zona parenchymatosa). The rete ovarii develops from the rete mass and does not, according to Felix, connect with the mesonephric tubules. The lateral portion of the ovary, containing the rete, is homologous with the superior pole of the testis. Degeneration of the central primary epithelial mass in the interior of the gonad supposedly early removes all of the gonadal or testicular material surrounding which the future ovarian cortex is formed. According to most textbooks the

*Read at a meeting of the Obstetrical Society of Philadelphia, October 7, 1937.

rete ovarii degenerates as well; Wilkerson, however, has shown the rete ovarii to be a normal constituent of the adult mammalian ovary.

Without becoming involved in a consideration of the complex problems of the determination, differentiation, and maintenance of sex and secondary sex characters, certain fundamental facts may be expressed: It is apparent that the gonads of all embryos are identical. In becoming testes the gonads suffer no radical alteration in original structure plan. On the other hand, ovary formation necessitates a later and secondarily superimposed addition of cortical tissue from the surface germinal epithelium upon the centrally displaced primary gonad. Further, male characteristics appear earlier than those of the female, a beautiful functional example of which is exhibited in the free martin. It follows, then, that the gonad is primarily male and that the female condition is a secondary one. Recent biologic concept tends to strongly favor this interpretation. If a hermaphroditic or bisexual condition is existent, it must be ascribed to the female since there the sex gland possesses the primary gonad (male) as well as the secondarily added, ovarian material.

Under certain normal developmental influences one sex predominates, such predominance being manifested by the definitive structure of the genital organs and secondary sexual characters. It is probable that completeness in reciprocal degeneration and growth is rarely produced and that varying degrees of low grade intersexuality occur normally, as evidenced by rests of primary gonadal material in the ovary and vestiges of the two paired ducts in both sexes. Evidence from the ovotestis in certain intersexual conditions likewise indicates that total degeneration of the primary gonadal tissue did not take place, since material capable of producing testicular tissue must have been left. Therefore, the extent of the degeneration or retention of this material in development is most significant. Such embryonic tissue would be expected, within normal limits of variation, to be found in the lateral half of the hilus of the ovary—in a position corresponding to the mediastinum (and its contents) of the testis with which its homology is apparent. The possibility is present, then, of the persistence of gonadal remains in all ovaries, and particularly in cases exhibiting degrees of male characteristics. This investigation was undertaken in an attempt to determine if such is actually the case.

Ovaries taken at autopsy from normal women (14 to 44 years of age) were sectioned serially and studied.* The rete ovarii was found to be present in all cases. It is located usually in the lateral half of the hilus of the ovary (Fig. 1), although many times it extends into the adjacent mesovarium to attach to the tubules of the epoophoron (70 per cent). Intimately related to the rete ovarii groups of epithelioid cells strikingly similar to interstitial cells of the testis and epididymis are regularly encountered. When present in moderate amount, they are always in the

*Grateful acknowledgement is made to Dr. Martin J. Crane for his generous cooperation in this study.

vicinity of the rete (Fig. 1), but when occurring in increased numbers, they may be scattered throughout the ovarian hilus and the related mesovarium as well (Fig. 2).

These cells have been mentioned by other investigators. Wallart has illustrated cells, labelled "paraganglionic," near the rete ovarii and usually at the lateral pole of the ovary. Berger has termed them "sympathicotropic cells" and believes them to be related to the sympathetic nervous system. Kohn has pointed out their similarity to male interstitial cells and feels that they should be compared to the extra-



Fig. 1.—Photograph of a mass of male interstitial cells adjacent to the rete ovarii in an ovary from a 44-year-old woman. Magnification 100 \times .

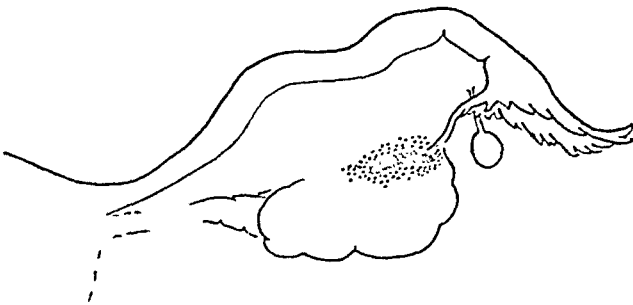


Fig. 2.—Drawing of the ovary to illustrate the position of the rete ovarii and interstitial cells. The closely lined area represents the usual position of the rete. The distribution of interstitial cells is shown by stippling.

glandular interstitial cells of the testis. Also, Kohn believes these cells to originate from the germinal epithelium. The contention that we are dealing with sympathetic or chromaffin tissue is seriously questioned after cytologic study. Female interstitial cells originate from the connective tissue theca during the atresia of ovarian follicles (Kingsbury) and rarely come to lie in the hilus or the mesovarium. Further, since female interstitial cells are extremely infrequent in the human ovary and are easily recognizable when present, it is impossible that they are being dealt with here. Adrenal cortical tissue was not encountered in these ovaries.

Attached to the rete ovarii in the lateral portion of the hilus of an ovary from a 34-year-old woman exhibiting signs of virilism, there were found a number of epithelial cords which strongly suggest medullary cords of the gonad and the testis cords of the primitive testis (Fig. 4). In this structure no cells which could be identified with certainty as germinal or Sertoli cells were seen.

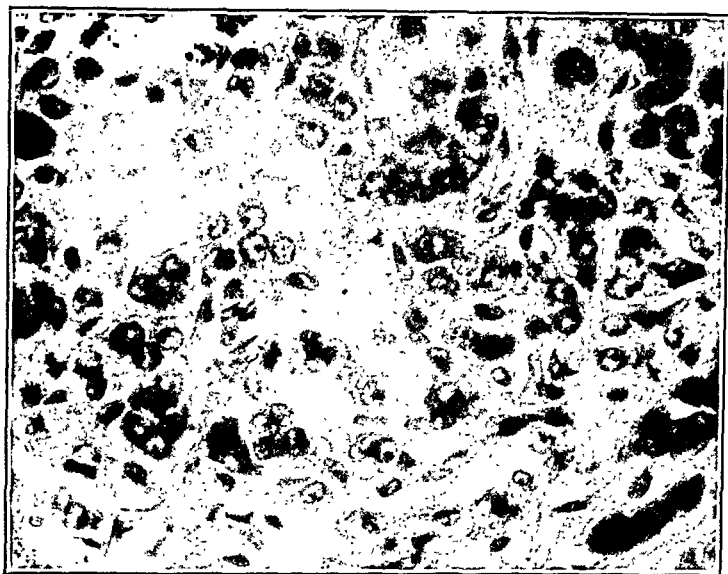


Fig. 3.—Photograph of male interstitial cells from the region of the rete ovarii in an ovary from a 22-year-old woman. Magnification 500 \times .



Fig. 4.—Photograph of epithelial cords attached to the rete ovarii from a 34-year-old woman. This structure was found in the lateral pole of the ovarian hilus. Magnification 100 \times .

There is a correlation between the amount of retained vestigial mesonephric material (actually male duct material) in the ovaries of normal women and the amount of rete ovarii and associated cellular formations. Ovaries related to large masses of epoophoron, paroophoron, cystic remains of Gartner's duct, etc., usually possess large accumulations of primary gonadal remains as well. Such findings are in keep-

ing with those prevailing in certain intersex conditions and are interpreted as being due to the activity, probably hormonal, of retained primary gonadal (essentially testicular) tissue which affects retention, growth, and differentiation of the male duct representatives as well as producing possible changes in the genitalia and secondary sex characters.

CONCLUSIONS

The ovary, particularly early in development, is interpreted as essentially bisexual, and in this is subject to wide individual variation.

Both the cellular elements described previously, interstitial cells and rudimentary testis tubules, are considered here to represent undegenerated gonadal materials which have become definitely testicular in direction of differentiation. In the light of the evidence obtained from this study the primary condition of the gonad is believed to be male. Other factors pertinent to the problem of sex must, for obvious reasons, be omitted here.

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ELEVENTH AND CLINTON STREETS
1534 PINE STREET

VIRILISM AND FEMALE PSEUDOHERMAPHRODITISM WITH RELATION TO THE BISEXUAL NATURE OF THE OVARY*

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THE manifestations of virilism range from slight facial hypertrichosis in otherwise normal women to such malelike characteristics as abundant growth of hair on the face, chest, abdomen and extremities, hypertrophy of the larynx, deepening of the voice, regression of the breasts, and enlargement of the clitoris. The menstrual function may be markedly disturbed or totally suppressed.

Pronounced types of virilism may occur as the result of tumors of the basophilic cells of the anterior pituitary, the cortex of the adrenal or the medulla of the ovary. Such lesions should be suspected particularly when symptoms of virilism arise in children or adult women or if an existing virilism becomes accentuated.

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In what may be called the ordinary form of virilism, the abnormal secondary sex characteristics appear at about the age of puberty, reach their maximum during adolescence, and then remain stationary.

Female pseudohermaphroditism is a condition in which the external genitalia resemble the male type, although the ovaries and other internal genital organs appear to be structurally normal. Virilism usually occurs during adolescence in female pseudohermaphrodites and creates additional difficulty in the recognition of the true sex.

Ordinarily the common form of virilism and female pseudohermaphroditism are not considered to be related conditions but the one may be regarded as an adult form of masculinization and the other a fetal type of the same phenomenon. In this light these two abnormalities will be discussed with relation to the bisexual nature of the ovary.

Pertinent to this discussion are certain factors concerning arrhenoblastomas, often called masculinizing tumors, which originate from the medulla of the ovary. Meyer describes two types of these neoplasms, one in which epithelial lined tubules are prominent and another composed of rudimentary cords of cells; and says that the latter type is invariably accompanied by marked physical signs of masculinization while with the former such effects may be slight or absent. McLester expresses this seemingly paradoxical relation by stating that those tumors with the least microscopic resemblance to testis show the greatest masculinizing effects.

A somewhat similar situation, although not so sharply defined, exists in the two forms of intersexuality of fetal origin encountered in women; both present the common feature of varying degrees of malelike formation of the external genitalia. But in true hermaphroditism, in which an ovotestis is present, there may be a little evidence of somatic intersexuality, i.e., the body form and breasts may be feminine in configuration; while in female pseudohermaphroditism, a condition in which the ovaries are apparently normal, the body form, especially the upper portion, and the breasts, may closely resemble the male type. Furthermore, at adolescence in the first instance beard growth may be slight or may not occur while in the second it is likely to be pronounced. An example of each of these types will be described in a later section of this paper.

In view of this peculiar distinction in the abnormal sex hormone effects which characterize the two types of these abnormalities, a consideration of certain etiologic factors is of interest.

Meyer believes that arrhenoblastomas originate from undifferentiated germ cells which are not utilized during embryonic development but which retain their sexual potency and under certain external conditions of unknown nature start to proliferate, and then only begin to exert an influence in the direction toward maleness.

This view is based upon the thought that the primary gonad, which is common to both sexes, is composed of physiologically indifferent cells, which, however, are inherently capable of development into either of the two distinctive sex glands. If this is true it then follows that a

condition of potential hermaphroditism exists during this early stage of gonadal development in every embryo.

This conception is no longer biologically acceptable. Certain animal experimental findings indicate rather that the primary gonad, in both sexes, is testicular in nature. In males it develops into a testicle. In females the cortex of the ovary arises from other cells which grow around the primary gonad which is eventually reduced, theoretically, to a vestigial state.

With regard to this subject Willier, for example, states that it is clear from the structure of the ovary of birds and mammals that it has a bisexual organization. The first set of sex cords which constitute the medulla is morphologically equivalent to the sex cords of a testis, whereas the cortex is distinctly peculiar to the ovary. Moreover, the medulla is potentially a testis as it has been possible to stimulate the first sex cords to form seminiferous tubules. True hermaphroditism, therefore, occurs only in those animals that were destined to be female and is essentially a condition of abnormal development of the primary gonad.

This conception is the more applicable to the conditions of sex reversal encountered in human beings with regard both to diagnosis and therapy. The weight of clinical evidence supports the view that in man, as in the higher animals, true hermaphroditism occurs only in those who are female in the genetic sense.

Another indication that the human ovary is bisexual in nature is the fact that testis hormone seems to be a constant constituent of the urine of women. The crude urinary extracts of testis hormone, which when injected into cacons cause increase in the size of the comb, are now called androgens. Various workers have found androgen in the urine of normal women in amounts approximately equal to those found in the urine of men.

In cases of virilism this substance is present in the urine in amounts appreciably greater than found in the urine of men according to the studies of Bühler; Simpson, de Fremery and Macbeth; and McCahey, Hansen, and Soloway.

The last named also studied the androgen content of the urine in two cases of hermaphroditism, in both of which the external genitalia simulated the male type. In one case the body form was masculine, the breasts were flat, and hair growth was present on the face to a degree which necessitated frequent shaving. Assays of the urine for androgen showed it to be present in amounts greatly in excess of those found in men. Operation by Dr. Catherine Macfarlane, at the Women's Medical College Hospital, showed the uterus to be small but the tubes and ovaries appeared to be normal. Section of the cortex of one of the ovaries was reported normal ovarian tissue.

In the other case the general body configuration was feminine, the breasts were developed, and there was only scant growth of hair on some parts of the cheeks. Androgen was present in the urine in amounts approximately equal to those found in normal men. Operation by Dr. E. L. Eliason, at the Philadelphia General Hospital, disclosed an

undeveloped uterus and an abnormal appearing gonad on one side which on microscopic examination was identified as an ovotestis.

These two cases are illustrations of the observation that female pseudohermaphroditism may exhibit more marked stigmas of somatic masculinization of both fetal and adult origin than true or glandular hermaphroditism.

From what has been said with regard to the equality of testis hormone elimination in the urine of both normal women and normal men, it might appear that rudimentary remnants of primordial testis tissue in the ovary possess an endocrine function as potent as that of normal testes. However, the degree of utilization must be considered. The androgen found in the urine of normal women may represent the entire amount elaborated while that found in the urine of men may represent only the portion of the total secreted which was not utilized in the maintenance of the male gonads and the accessory sex apparatus.

The factor of utilization is probably also of significance in connection with the relatively slight masculinizing effects in the two affections of women associated with the presence of testis-like tissue, namely, the tubular form of arrhenoblastomas and glandular hermaphroditism. It is reasonable to suppose that the major portion of the elaborated hormone is utilized in the maintenance of these seminiferous tubular structures.

With regard to the occurrence of more marked signs of masculinization with both the cellular form of arrhenoblastomas and female pseudohermaphroditism certain questions arise: Are the abnormal sex accompaniments of both due to endocrine activity of embryologically analogous cells of primary gonadal origin? Are such cellular structures present in the ovaries in cases of female pseudohermaphroditism and the common form of virilism?

That such tissue is present in the ovary in both these conditions appears to be a reasonable supposition solely on the basis of the clinical features which have been discussed. Testis hormone investigations lend further support to this view, although the evidence with respect to these is incomplete because of the paucity of such studies from the standpoint of clinical investigation.

The possibility of the presence of testis-like tissue in the ovary is frequently mentioned in articles dealing with conditions of sex reversal in man, but such references have been with regard to the rete ovarii, which is analogous with the rete testis, a structure which has to do with neither spermatogenesis nor hormone secretion. The rete ovarii is a well-recognized embryologic structure but the usual teaching is that it disappears at birth although occasionally it persists until puberty.

In the investigations of this problem carried out by Ramsay and McCahey, the rete ovarii was found in all the ovaries of normal adult women which were examined and in association with it there were cells apparently similar to the interstitial cells of the testis. In an ovary from a case of virilism, a structure composed of cells in an arrangement strongly suggestive of rudimentary testicular tubules or gonadal medullary cords was found connected with the lateral portion of the rete.

close relationship which must be fulfilled between exposure and mid-period low temperature with its implied ovulation in order to ensure conception. Exposure has apparently little chance of prematurely rupturing the ovarian follicle, since this woman had exposures in several months on the day before the temperature rise began but pregnancy did not ensue. She became pregnant, however, the first time she had an exposure on the day after the rise began. This would indicate that the viability of the sperm is less than twenty-four hours.

In other women studied, repeated exposure just after the low temperature level failed to produce pregnancy; this indicates a viability of the ovum of not more than thirty-six hours.

It will also be observed from this record that a subsequent full menstruation occurred after pregnancy had started and that conception took place fourteen days before the onset of the period. This particular woman also menstruated once after a preceding pregnancy.

The human fertile period is herein shown to vary from woman to woman and from cycle to cycle. It is necessary to study each woman's variation in order to understand her particular variability. As a simple method of determining the time of ovulation, the basal rectal temperature is offered, since it is a procedure which is easy to follow and since it bears a close relationship to the time of ovulation as shown by the above reported case records.

SUMMARY

1. In 35 cases herein reported conception occurred from the tenth to the twentieth days of the menstrual cycle regardless of cycle length.

2. Basal body temperature is a guide to the period of fertility as identified in these studies to occur not more than three days before or one day after the midperiod of the menstrual cycle, with a high incidence at the time of the last low temperature before the lutein phase begins.

3. Breast tenderness of unusual severity occurs before the missed menstrual period, and the morning sickness of pregnancy begins at the time of the next ovulation period after conception starts.

4. The viability of both sperm and ovum is short, probably not exceeding twenty-four hours.

5. Intercourse does not cause follicle rupture.

6. Ovulation and menstruation may occur after conception begins.

7. Studies of basal body temperature may be used as a guide or forecast of unusual ovulations or to supplement other data in studying sterility. There is advantage in this type of study where menstrual physiology is obscure.

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length. In no woman did pregnancy occur more than three days before or one day beyond the initial rise of temperature from the midperiod low level. After conception the temperature no longer undergoes a cyclic change except in those few women who menstruate or perhaps even ovulate after pregnancy starts. The temperature during pregnancy remains high as in the last part of the menstrual cycle and can be used as a sign of pregnancy before other methods of diagnosis are positive. From the records of these women we find it possible to diagnose pregnancy also by a persistent tenderness of the breasts more pronounced than that usual in the premenstrual days. This exaggerated

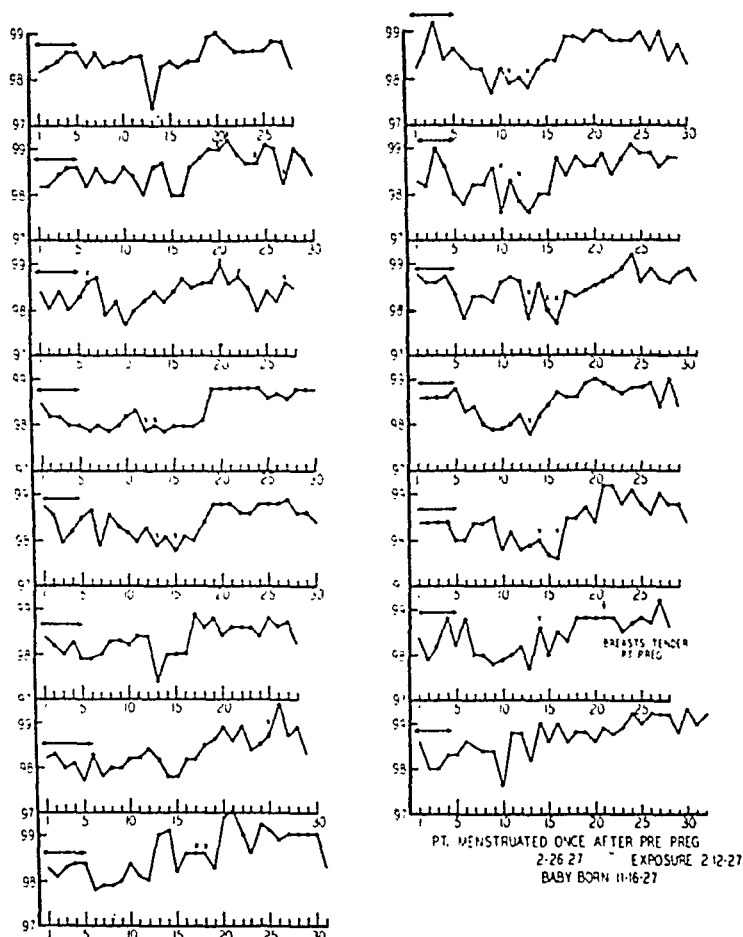


Fig. 5.—The temperature and exposure records of one woman over fifteen menstrual months preceding pregnancy to illustrate the close relationship between exposure and midperiod low temperature with its implied ovulation which must be fulfilled in order to ensure conception.

tenderness always appears before the missed menstrual period. In one woman it occurred on the fifth day after exposure, a finding which suggests an occasional earlier date for implantation than the tenth day after fertilization as claimed by Hartman.⁹

In every woman the morning nausea started at what by computation would be the date of the next ovulation after conception. Hence morning sickness of pregnancy may be related to a change in the ovulation cycle.

Fig. 5 represents the temperature and exposure records of one woman over fifteen menstrual months preceding pregnancy to illustrate the

METHODS

Estrogenic hormone determinations were done exactly as described in previous reports.^{3, 4} The urine was not extracted for "free" estrogenic hormone, however, until the sixth week of pregnancy. In all instances the estrogenic hormone was calculated as estrone in gamma excreted per day.

Gonadotropic hormone determinations were done each week according to a concentration method described by Freed and Hechter,⁵ until the hormone characteristic of pregnancy first became evident. After pregnancy was established the whole and diluted urine was tested for its gonadotropin content. A mouse unit of the gonadotropic hormone characteristic of pregnancy is the least amount of hormone necessary to produce at least one corpus luteum in at least one ovary of a nineteen to twenty-one-day-old female mouse 100 hours after injection. The amount excreted per day was calculated from the twenty-four-hour volume of urine.

DISCUSSION

As noted in the chart the first positive pregnancy reaction was obtained at the end of the second week of pregnancy, which date should have been the day of onset of the first missed menstrual period. The first demonstrable excess in the excretion of estrogenic hormone occurred at the end of the sixth week of pregnancy. The early appearance of the gonadotropic hormone characteristic of pregnancy as compared with the later appearance of increased amounts of estrogenic hormone is of importance in understanding why pregnancy tests which depend upon the detection of gonadotropic hormone are of greater value in early pregnancy than those tests which depend upon the detection of increased excretion of estrogenic hormone.

The peak of gonadotropic hormone excretion occurred at the end of the sixth week of pregnancy. The amount is in agreement with the reports of other investigators.⁶⁻⁹ Although the patient experienced morning nausea, the latter did not seem to have a clear-cut association with the peak of gonadotropic hormone excretion.⁶ This marked excretion of gonadotropic hormone demonstrates the impossibility of making a diagnosis of hydatidiform mole and chorioepithelioma on the basis of quantitative hormone excretion during the first trimester.

The fall of gonadotropic hormone excretion during the eighth and ninth weeks, followed by a second rise, has not been reported previously. Similar studies of habitual abortion may help to determine whether or not this phenomenon may be associated with a patient's tendency to abort.

The urine concentration procedure failed to reveal any of the gonadotropic hormone in the urine later than the fifth day post partum.

Five days before the patient aborted, the excretion of estrogenic hormone fell far below the expected gradually rising level known to occur in normal pregnancy. Could this have been known on the day of its occurrence, some form of hormone therapy might have prevented the termination of pregnancy. Chemical tests for estrogenic hormone which may be done quite rapidly are not, as yet, of definite value so early in pregnancy.

With reference to the second point in the purpose of this report, namely the confirmation of findings reported by Cohen and others,¹ the

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EXCRETION OF HORMONES IN A CASE OF HABITUAL ABORTION*

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THE purpose of this report is twofold; first to present the urinary estrogenic and gonadotropic hormone findings in a carefully followed case of abortion, and second, to confirm the findings of a report by Cohen and others,¹ and Marrian² in which an association between the sudden excretion of free fat-soluble estrogenic hormone and the onset of labor was demonstrated.

The patient studied was a woman of 36 years, anxious to have a child but with the history of two spontaneous abortions at 1.5 and 5 months and one premature labor at 6.5 months in the order noted. The latter pregnancy terminated spontaneously Jan. 8, 1936. It was planned at that time that the patient should collect complete twenty-four-hour urine specimens regularly at weekly intervals during the ensuing year and bring them to the laboratory for the assay of estrogenic and gonadotropic hormones. She was to avoid pregnancy for the first six months of this experiment. This plan was carefully followed. A daily record of intercourse and menstrual periods was kept.

The intervals at which coitus occurred, the date of abortion, and the size of the fetus were such that the probable date of conception could be quite accurately calculated. Unfortunately for the patient the pregnancy under investigation was multiple (twins) and an examination within a few hours after the earliest symptoms of abortion revealed a bulging amnion filling the vaginal vault. The patient promptly aborted twins and subsequently recovered after a stormy four-day febrile reaction.

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sudden excretion of increased amounts of "free" fat-soluble estrogenic hormone preceded and accompanied parturition. Cohen fractionated the fat-soluble estrogenic hormone into estrone and estriol for purposes of chemical identification. This procedure does not, at the present time, lend itself well to biologic means of testing. The "free" estrogenic hormone shown in the accompanying chart represents both estrone and estriol whose joint estrogenic activity is calculated as estrone.

It should be stated that the small amounts of "free" hormone excreted from the seventh week until the week during which parturition occurred are probably of no significance. Although each specimen was extracted within twenty-four hours of its collection, slight bacterial hydrolysis of "combined" hormone is known to occur in the urine upon standing at room temperature. The time factor is a constant one in this laboratory.

The rather marked fall in urinary hormone excretion at the onset of labor is in keeping with a suggestion made in a previous report,⁴ namely that the uterus may be considered an excretory organ for estrogenic hormone.

SUMMARY

The quantitative hormone determinations and discussion pertaining to them in a case of habitual abortion are presented. The relationship of estrogenic hormone excretion to parturition is demonstrated.

CONCLUSIONS

1. Parturition is accompanied by a sudden urinary excretion of "free" fat-soluble estrogenic hormone.

2. The diagnosis of hydatidiform mole or chorionepithelioma cannot be made from the quantitative determination of gonadotropic hormone excretion in the urine during the first trimester.

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The author feels that the first stage of labor begins not when uterine pains begin but during the last few weeks of pregnancy, with a slow and gradual formation of the lower uterine segment. Undivided control over the latter weeks of pregnancy and the succeeding labor would serve greatly to lessen complications. Quinine is recommended for prophylactic use where a uterine inertia is threatened in the first stage. He recommends Dührssen's incisions or spinal anesthesia and manual dilatation for the slowly dilating cervix.

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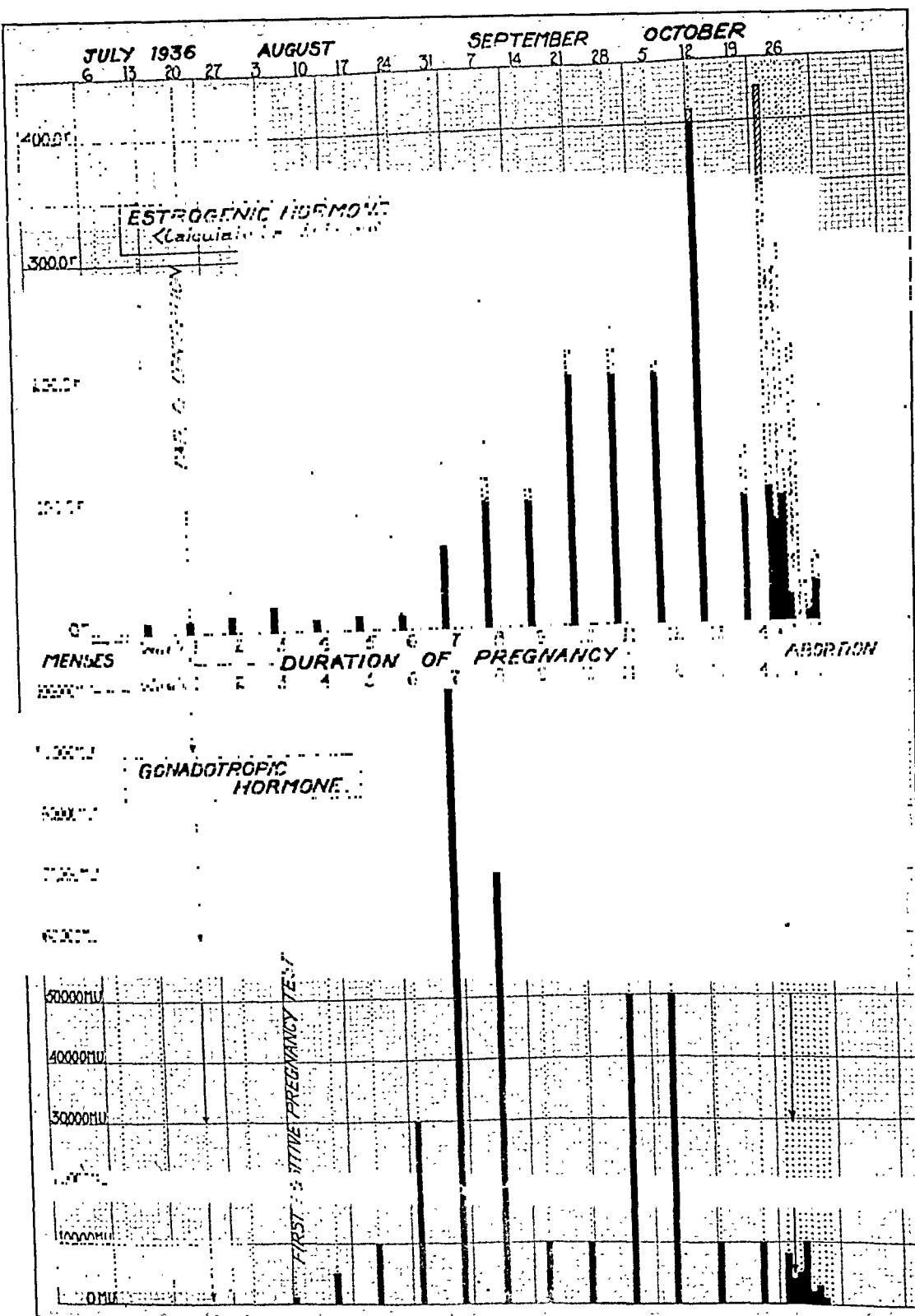


Chart 1.—*Estrogenic Hormone*: The columns represent the total excretion of estrogenic hormone per twenty-four hours on the days indicated. The solid portion of the column represents the "combined" fat-insoluble hormone, and the shaded portion of "free" fat-soluble hormone. Each is calculated as estrone. *Gonadotropic Hormone*: The columns represent the total excretion of the gonadotropic characteristic of pregnancy per twenty-four hours on the days indicated. In every instance the assay was done on a portion of the same twenty-four-hour urine specimen used for estrogenic hormone determination. A mouse unit is the least amount of hormone necessary to produce at least one corpus luteum in at least one ovary of a nineteen to twenty-one-day-old female mouse 100 hours after injection. The amount excreted per day was calculated from the twenty-four-hour volume of urine.

Incidence.—Compared with other varieties of complication of gonorrhea in the female, rupture of a pyosalpinx is rather infrequent. Norris¹⁹ states, "Rupture or perforation of an adherent pyosalpinx into the rectum is not infrequent and into the bladder or upper intestine is more rare. Rupture into the peritoneal cavity seldom occurs." Curtis⁷ in his recent text, states, "The danger of tubal rupture comparable with rupture of the diseased appendix, is sometimes emphasized to patients as a reason for surgical intervention. The possibility of this complication is remote. I believe it has not occurred in any of our patients." Yet from the two cases seen by us in a two-year period, and a statistical survey of the literature, it would appear to be a not infrequent occurrence and one certainly to be kept in mind, for upon its early recognition depends a good prognosis.

Lenormand and Kaufman¹⁵ state that of 560 patients with all types of salpingitis operated upon, there were 5 in which rupture of the tube was noted, giving an incidence of approximately 1 per cent. But, of the patients with generalized peritonitis operated upon due to all causes, five were caused by ruptured pyosalpinx, giving an incidence of 8 per cent. Similarly, Bauer² in the Scandinavian literature reported 138 cases of generalized peritonitis, 115 of which were due to appendicitis, 13 to ruptured ulcer, and 10 to perforation of the pyosalpinx, giving again an approximate incidence of 8 per cent to all cases of generalized peritonitis.

ETIOLOGY

Immediate Cause for Rupture.—In the majority of cases, there is no assignable cause for rupture, i.e., it occurs spontaneously, as in the two cases to be reported. Of the 102 cases gathered by Petroff²⁰ 56 cases occurred spontaneously. In these cases, it is the increasing distention of the pus tube by the acute inflammation with secondary ulceration of the wall of the tube which is the predisposing factor which leads to the perforation.

In a minority of cases, some form of direct or indirect trauma is immediately responsible for the perforation. Among these direct acts of violence may be a kick or blow on the vulva, perineum or lower abdomen, or ill-advised or too vigorous bimanual examination (Leguey,¹⁴ Martin¹⁸) or violent coitus or trauma incident to a curettage which is subsequently diagnosed as a puerperal infection. Among the indirect causes of trauma responsible for the rupture, may be mentioned the pregnant uterus, which as it enlarges, pulls up and thins out an adherent inflammatory tube, or labor itself, with its incident muscular efforts (Tait²³). Other indirect exciting causes are straining, lifting, or the use of violent purgatives (Janeway¹²) or transportation to a hospital (Mann¹⁷).

Age.—The age period during which the condition was found to occur most frequently is that period when active pelvic infection is most common, namely, between the ages of twenty and forty years. In Petroff's 102 cases, 66 per cent occurred in this age group, with extremes of sixteen and fifty-four years.

Size, Location, Duration of Pyosalpinx and Point of Perforation.—No rule can be made as to the size the pyosalpinx must attain before it is likely to rupture. In many of the reported cases, they have been small, and in others the pyosalpinx attained a large size. Nor are there sufficient data in many of the reports to determine the duration of the pyosalpinx and the number of attacks that have occurred prior to rupture. It is true that recent acute exacerbations of the chronic pelvic disease undoubtedly predispose to rupture by bringing about an increasing distention and ulceration of the pus tube.

Interestingly enough, rupture occurs somewhat more frequently on the right side than on the left, although in all cases, the opposite tube is also diseased. Brickner⁵ states that rupture occurred 33 times in the right tube and 23 times in the left, and Petroff gives 54 cases as occurring on the right side and 42 on the left. The perforation occurs most frequently in the ampullary end of the tube and the size of

GENERALIZED PERITONITIS SECONDARY TO RUPTURED PYOSALPINX

WITH THE REPORT OF TWO CASES

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GENERALIZED peritonitis secondary to chronic pelvic inflammatory disease may occur by one of two methods: The purulent material may be expressed from the patent fimbriated ostium of the tube and then spread over the general peritoneal cavity, or the material may be suddenly discharged by rupture of a pyosalpinx. It is the latter condition which forms the basis of this paper. Here the infection starts as an endosalpingitis, usually caused by the gonococcus. The tube then becomes sealed off at both ends and undergoes increasing distention until it becomes a cystic mass containing pus. The pyosalpinx may then burst either spontaneously or as a result of some slight, indirect trauma, liberating its purulent material into the general peritoneal cavity.

The purpose of this paper is to emphasize the clinical syndrome associated with this condition, and to offer suggestions for its treatment, based on a survey of the cases previously reported.

HISTORY

Gendrin¹⁰ in 1833, was the first to observe that rupture of a pyosalpinx may give rise to a generalized peritonitis. In this case, reported in 1844, the pyosalpinx was probably not of gonorrheal origin, but rather secondary to a septic abortion which preceded the perforation. Later, in 1861, M. Chipault⁶ presented a case before the Société Anatomie de Paris; here the pyosalpinx was probably caused by an advanced carcinoma of the cervix which the patient presented, and not by a gonorrheal infection. The following year before this same society, Almagnon¹ presented the autopsy findings of a case of generalized peritonitis secondary to rupture of an enormously distended pus tube. This case too, was probably of postabortal, rather than gonorrheal origin. Lawson Tait²² in 1889, described a case seen twenty years previously, of ruptured pyosalpinx, which he attributed to the repeated use of mechanical pessaries.

The first case of gonorrheal pyosalpinx to be reported was that of Lawson Tait.²³ This was not, however, a spontaneous rupture but occurred during the course of labor. The patient was thought to have "puerperal fever" until autopsy disclosed her death to be due to rupture of a gonorrheal pyosalpinx, occurring during labor. The first reported case of gonorrheal pyosalpinx rupturing spontaneously should be attributed to Bernutz,²⁴ who read his paper before the Société Anatomique, on Jan. 16, 1880. During the same year, Janeway¹² in this country, reported a similar case discovered at autopsy. In 1913, Norris¹⁹ summarized the literature to that time and brought the total reported cases to 97. Subsequently, infrequent reports of this condition have appeared in the American literature. Petroff²⁰ in 1932 collected 102 cases from the French literature. In 1935, Soimaru²¹ reported five cases seen in a short time. In Germany, Lübke¹⁶ reported 34 cases seen at the Eppendorf clinic between 1900 and 1934. The sum total of these cases in the literature brings the total to approximately 238. This figure probably grossly underestimates the exact frequency of this condition. There are perhaps a considerable number of cases not recognized clinically, or recognized, but not reported.

A number of cases of ruptured pyosalpinx have been mistaken for ruptured appendicitis with generalized peritonitis, but the history in the latter, before perforation is very important. Fortunately the treatment of all of these cases for which rupture is likely to be mistaken, is the same, namely operation.

TREATMENT

The treatment of cases of ruptured pyosalpinx as seen from a study of the cases in the literature is primarily surgical. All cases of ruptured pyosalpinx, or those suspected as such, should be subjected to immediate operation. There is no single case on record of survival without operation. Of the 91 cases collected by Brickner⁵ in 1912, 36 patients were not operated upon and all died.

As to the nature of operation to be performed, it appears from Table I that salpingectomy is the procedure of choice, for it is associated with the lowest mortality.

TABLE I. OPERATIVE PROCEDURES AND RESULTS

NATURE OF OPERATION	NUMBER CASES	DIED	MORTALITY PER CENT
1. <i>Drainage Alone:</i>			
Petroff ²⁰	9	6	66
Soimaru ²¹	5	3	60
2. <i>Unilateral or</i>			
<i>Bilateral Salpingectomy:</i>			
Petroff ²⁰	46	10	21
Soimaru ²¹	28	3	11
Duval ⁹	12	1	9
3. <i>Subtotal or Total</i>			
<i>Hysterectomy:</i>			
Petroff ²⁰	30	7	23
Soimaru ²¹	11	4	36

Bilateral salpingectomy with removal of all of the diseased tissue, appears to be a safer procedure than a unilateral salpingectomy alone, for it is associated with a lower mortality rate. (Petroff,²⁰ 11.8 per cent against 27.5 per cent.) Adequate drainage from the pelvis should be instituted by Mikulicz' drain or rubber tube drain. It is only with such treatment that these patients having a ruptured pyosalpinx may be saved.

PROGNOSIS

From a review of the cases previously reported in the literature, it is interesting to note that the general mortality in all cases of ruptured pyosalpinx has gradually and progressively declined. This is well illustrated in Table II which shows the original mortality of 50 to 60 per cent to have declined to approximately 20 per cent in the course of the last twenty-five years.

The prognosis in any given case depends on a variety of factors. It is generally agreed by all authors that one of the most important factors is the time at which surgical treatment is instituted. There is not a single case on record of recovery without surgical intervention, and most

the perforation may be from a few millimeters to several centimeters in diameter.

Organism.—In practically all cases of chronic pelvic disease, it is the gonococcus which is the primary offending organism. Subsequently, however, in its development, the pyosalpinx becomes secondarily infected with other organisms. The actual causal relationship of the gonococcus to the pyosalpinx has been difficult to demonstrate because of the overwhelming growth of these secondary invaders, because of the death of the gonococcus when the tube becomes sealed off at both ends, or perhaps because of the difficulty in culturing this organism. It is the secondary invasion of the pyosalpinx by other pathogenic organisms, that makes perforation so frequently fatal.

Brickner⁵ in a study of 91 cases, found 11 cases of perforated pyosalpinx to be of gonorrheal origin. Petroff found that of 17 cases examined bacteriologically after perforation, the *Streptococcus hemolyticus* and the colon bacillus were most common and that the gonococcus was present in only one case. Of Lübke's¹⁶ 34 cases, the gonococcus was demonstrated in two cases.

SYMPTOMS AND DIAGNOSIS

The symptoms vary widely, but for the most part, there is a definite clinical syndrome associated with ruptured pyosalpinx that can be diagnosed without difficulty. The onset is usually very abrupt and violent and the symptoms progress very rapidly, starting with a sudden sharp pain in the lower abdomen most marked over the site of the lesion, followed by the rapid development of a diffuse peritonitis with more or less marked collapse, a symptom complex, not unlike that of a ruptured ectopic pregnancy. Frequently, there are nausea and vomiting, associated with pallor and profuse perspiration. The patient complains of being chilly, and the extremities are cold. The temperature is normal or subnormal for a few hours with a coexisting rapid pulse. This disproportion between the temperature and the pulse rate in the early stage, is a suggestive sign. The temperature soon rises and other evidences of peritonitis rapidly become manifest. The abdomen shows at first, generalized marked rigidity, and later, abdominal distention. There is a definite leucocytosis of 12,000 to 20,000 white blood cells, and an elevated erythrocyte sedimentation rate.

The diagnosis, if one bears in mind the clinical picture, is not at all difficult, especially if one had examined the patient before rupture and knows the condition of the adnexa, their size, shape, and consistency. The history of the case, especially if there had been a previous gonorrheal infection and prolonged sterility, a careful abdominal and pelvic examination with special emphasis on signs of chronic gonorrhea, the disproportion between the temperature and pulse at the start with a subsequent mounting temperature, and signs of general peritonitis, together with a leucocytosis and an elevated erythrocyte sedimentation rate, should aid one in arriving at a correct diagnosis.

This condition may be confused with simple acute exacerbation of a chronic pelvic disease, torsion or rupture of an ovarian cyst, ruptured tubal pregnancy, and ruptured appendix. Rupture of a pyosalpinx may be distinguished from an acute exacerbation of a chronic salpingitis by the greater severity of its symptoms, the diffuse character of the infection, with the signs of collapse, and an increased sedimentation rate. Curiously enough, with an overwhelming infection in the form of a generalized peritonitis associated with the ruptured pyosalpinx, the sedimentation rate appears to be slower than in localized simple acute salpingitis.

The clinical picture of torsion or rupture of an ovarian cyst is very similar to that of a ruptured pyosalpinx. This, however, it should be easy to differentiate by a careful history and pelvic examination, noting the presence or absence of gonorrhea in the lower genital tract.

A ruptured tubal pregnancy offers difficult problems in differential diagnosis. In this condition however, one does not often find evidence of chronic pelvic inflammatory disease, hyperpyrexia, or marked abdominal rigidity, but does find evidence of an internal abdominal hemorrhage and secondary signs of early pregnancy.

In the majority of specimens studied, these structures were situated in the hilus of the ovary in the lateral half and sometimes extending into the adjacent mesovarium.

As the location of this tissue was usually found to be such that extirpation appears to be feasible, the suggestion seems warranted that further study may show that beneficial results may be obtained in cases of both female pseudohermaphroditism and the common form of virilism by surgical removal of the lateral portion of the ovaries including the hilus and adjacent portions of the mesovarium.

With regard to those cases of virilism dependent upon tumors of the adrenal or the anterior pituitary, it is not clear whether the masculinizing effects are primary or secondary. Neither of these glands are known to secrete a sex hormone, but in the case of the anterior pituitary, a sex-stimulating function is well established. Bruins Slot has recently reported a case of tumor of the left adrenal associated with virilism. A large amount of androgen was found in the urine, but assays of the tumor after removal failed to show the presence of either sex hormone.

The suggestion is made that those who have the opportunity to study such cases at autopsy examine the ovaries with reference to the cellular structures around the rete ovarii.

CONCLUSIONS

1. It is suggested that, in cases of the common form of virilism and cases of female pseudohermaphroditism, study of the ovaries for the presence and location of primordial testis tissue be made with the view of determining the possible advantage of removing this tissue by surgical means.

2. The suggestion is made that when cases of virilism associated with tumors of the adrenal or anterior pituitary come to autopsy that examination of the indicated portions of the ovaries be made part of the routine investigation in order to ascertain the relation of these cells to the primary growths.

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1534 PINE STREET

ELEVENTH AND CLINTON STREETS

DISCUSSION ON PAPERS BY RAMSAY AND McCAHEY, AND BY McCAHEY AND RAMSAY

DR. DAVID M. DAVIS.—There is so little about the gonads which can be proved from their histologic appearance. We hear, for example, about ovarian interstitial cells. These apparently arise from the cells of the theca and are therefore entirely different from the interstitial cells in the male. They are sometimes present in small numbers in the adult, but there is no way in which their function can be

TABLE II. MORTALITY STATISTICS

AUTHOR	YEAR	CASES	NUMBER DIED	MORTALITY PER CENT
Bonney ³	1909	45	22	48
Bovée ⁴	1910	56	32	57
Brickner ⁵	1912	91	56	61
Lamouroux ¹³	1912	27	9	33
Lübke ¹⁶	1924	34	14	41
Duval ⁹	1929	14	1	7
Petroff ²⁰	1932	102	28	27
Soimaru ²¹	1935	5	1	20

patients operated upon after forty-eight hours from the onset of the acute symptoms, die. The duration of survival without operation may be anywhere from a few hours to three and one-half months, with an average of fifty-nine hours.

The percentage mortality in all cases of ruptured pyosalpinx varies directly with the length of time before surgical intervention. In Brickner's⁵ series of those operated upon within twelve hours, 10 per cent died, and 90 per cent recovered. Similarly, in Lübke's series, the percentage mortality was 27 per cent in those operated upon within the first twelve hours. Huet¹¹ gives 10 per cent mortality and Petroff²⁰ gives 18 per cent mortality, with a corrected mortality of 11.8 per cent within this twelve-hour period. The mortality, however, in the operative cases rises rapidly with each hour elapsing, as shown by Petroff²⁰ in Table III.

TABLE III. MORTALITY ACCORDING TO TIME OF OPERATION (AFTER PETROFF²⁰)

HOUR OF SURGICAL INTERVENTION	NO. CASES	NO. RECOVERIES	NO. DIED	MORTALITY PER CENT
Before 12 hours	34	28	6	18
Between 12 and 24 hours	20	15	5	25
Between 24 and 48 hours	9	6	3	33
After 48 hours	11	3	8	73

The only reason for Duval's excellent results (Table II) is the fact that those who survived were operated upon from six to forty hours after perforation, and the one patient that died had the perforation eight days prior to operation.

Another important factor upon which the prognosis depends is the type of surgical procedure instituted. The operation which is rapid and carried out with a minimum of trauma and manipulation and yet removes the entire pathology, is the procedure of choice. And this has been found, by all authors, to be a unilateral or bilateral salpingectomy with drainage. If other procedures are instituted at the time of operation, the mortality is much higher.

The character of the predominating organism is only of secondary prognostic importance. Generally, the streptococcus and the colon bacillus are most virulent and the cases in which the pus is sterile, or contains the gonococcus or staphylococcus, have a better prognosis. Of 11 patients operated upon within twenty-four hours, and in which the pathogenic organism was known, in Petroff's series,²⁰ all, except one, lived regardless of the character of the organism (and there were four which showed streptococci, others with colon bacilli, and colon bacilli

plus staphylococci and gonococci). In the patient who died, a streptococcus was recovered, but the patient died of postoperative hemorrhage following a second operation. On the other hand, of those patients operated upon after twenty-four hours, one patient who was infected with the colon bacillus lived and 5 others died. Of the latter there were 3 cases which showed streptococci, 1 enterococci, and 1 in which the organism was not identified. Of course, those cases in which the pus was sterile (1 case, and 5 cases in Lübke's series) survived, regardless of the time of operation.

It appears therefore, that for the most part, the prognosis depends upon, (1) the general state of the patient, (2) the time of surgical intervention, (3) the nature of the operation instituted, and (4) to a lesser extent, the bacteria present at the time of perforation.

REPORT OF CASES

The following is a report of the 2 cases observed in two successive years at Cumberland Hospital.

CASE 1.—History.—E. R., a 35-year-old white female, was admitted April 4, 1934 with the history of an onset of generalized cramplike pains associated with constipation, ten days prior to admission. For five days prior to admission, the patient had persistent vomiting associated with the abdominal pains. The day before admission she had had a bowel movement following an enema. Her menstrual history had always been regular; the last regular period started on March 22, 1934, and lasted one week as usual. She had again begun to bleed, however, five days prior to admission; this period came two weeks too early and was associated with a more profuse flow. Her past history revealed she had been married sixteen years, but had never been pregnant.

Examination.—On admission, the patient was anxious, in severe shock, and had cyanosis of the lips and nail beds. Her skin was cold and clammy, the pulse feeble, and her blood pressure unobtainable. The abdomen was markedly rigid in both lower quadrants with severe tenderness, especially in the left lower quadrant. Vaginal examination showed the cervix to be normal; the uterus was retroverted. There was tenderness in the right fornix and a tender mass was found obliterating the left fornix. The cervix was not tender to motion. Rectal examination disclosed a tender mass in the posterior cul-de-sac.

Laboratory Data.—There was a leucocytosis of 18,000 white blood cells, with the polymorphonuclear leucocytes 92 per cent. The sedimentation rate was 18 mm. in sixty minutes (normal, over two hours). The urine had numerous casts, epithelial cells, and white blood cells, albumin 2-plus, acetone 1-plus. Blood chemistry revealed urea nitrogen of 54.4 mg. per cent. Temperature on admission was 104° F. and subsequently rose to 106° and 107° F.

Course.—The patient remained in extreme shock in spite of active treatment with stimulants and parenteral fluids. She continued to vomit, and died ten hours after admission.

Autopsy Findings.—Autopsy revealed an acute diffuse suppurative peritonitis with a cul-de-sac abscess. There was an acute suppurative left salpingo-oophoritis with perforation, with an acute suppurative right salpingitis. The lungs revealed an interstitial pneumonia and atelectasis in both lower lobes.

Comment.—It is interesting to note that this woman gave a history of sterility of sixteen years duration. She probably sustained her gonorrheal infection very early in married life, following which she became sterile. She then harbored the chronic salpingitis until this acute exacerbation with perforation which ended in diffuse peritonitis and death. The history of obstinate constipation is interesting, and it was not infrequently met with, in the cases presented in the literature.

The purgation in an attempt to overcome the constipation was the final precipitating factor in bringing about increased congestion, engorgement, and finally perforation. The shock seen in this case was profound and is typical of the condition. The hyperpyrexia was preagonal though at the time of perforation, the temperature is usually normal or subnormal. The elevated urea nitrogen was probably of extra-renal origin resulting from dehydration secondary to the persistent vomiting of five days duration. Her condition on admission, which was ten days after the onset of the fulminating peritonitis, precluded any possible surgical intervention, and she died shortly afterwards.

CASE 2.—First Admission: History.—M. T. was first admitted on May 11, 1934 with a history of onset of sharp pain in the right lower quadrant, eleven days prior to admission, spreading gradually over the entire abdomen and associated with chills and fever. Her menstrual history was normal. She gave a history of vaginal discharge and dysuria of several years duration. One year prior to admission, a routine Wassermann was found to be positive and the patient was given six intramuscular injections.

Course.—The patient was placed on a course of Elliott treatments following which the pain and tenderness gradually subsided and she was discharged on May 24, 1934, with residual though no longer tender masses in both fornices. Her sedimentation rate was still rapid (18 mm. in fifteen minutes).

The patient was readmitted on Oct. 19, 1936, in a comatose condition with a history of having had abdominal pains with high fever, and persistent vomiting for four days prior to admission. According to the history obtained from her husband, she had become comatose and weak on the morning of admission.

Examination.—Physical examination at this time showed the patient to be in coma and shock with her extremities cold, though not perspiring. Her pupils were small and did not react to light. Blood pressure was 80/60, pulse 120 per minute, feeble and easily compressible. Heart sounds at the apex were poor. Examination of the abdomen was unreliable because of the patient's poor reaction to stimuli. There was rectus rigidity on the right side and lower abdomen, with questionable rebound tenderness. Vaginal examination disclosed the presence of sausage-shaped freely movable masses in the right fornix. On the left side there was a hard irregular mass of indefinable outline, which was apparently continuous with a mass in the anterior vaginal wall.

Laboratory Data and Course.—There was a leucocytosis of 13,200 white blood cells, with 86 per cent polymorphonuclear leucocytes. The sedimentation time, done by the same method as on previous admission, was now one hour. Urine showed 2-plus albumin. Routine blood chemistry revealed the sugar to be present in a concentration of 26 mg. per cent, and urea nitrogen 76.9 mg. per cent. The patient was given 50 c.c. of 50 per cent glucose intravenously, and five minutes later was sitting up in bed giving a fairly intelligent history. Her blood sugar at this time was 50 mg. per cent. She remained conscious but in a state of shock with blood pressure ranging between 70 and 90 mm. mercury systolic and 30 to 60 diastolic, and rapid pulse, in spite of continued administration of parenteral saline and glucose. On the third day after admission, the patient's condition improved and she appeared to be recovering from shock, but on the following day she presented signs of pneumonia in both lower lobes, and she died on the sixth day after her admission, with a terminal temperature of 106° F.

Autopsy Findings.—Autopsy revealed a generalized peritonitis secondary to a bilateral salpingitis with perforation of a right pyosalpinx. The pancreas was sclerotic and contained an adenoma of the islands of Langerhans. Lungs showed a terminal bronchopneumonia.

Comment.—This case is interesting in that the patient was treated at the hospital for an acute salpingitis, two years prior to the time of her perforation, and was discharged "improved" only to return with this fatal complication. The clinical picture of the second admission for the perforated pyosalpinx was both obscured and complicated by the presence of the adenoma of the pancreas, giving rise to the

hyper-insulinism, hypoglycemia and its incident coma. The hypoglycemia reacted spectacularly to the administration of glucose intravenously, but the shock, incident to the abdominal calamity, persisted for two days. This ultimately was complicated by a terminal bronchopneumonia and the patient died ten days after the onset of the acute symptoms. In this second case, the diagnosis of peritonitis secondary to ruptured pyosalpinx was entertained, but the additional findings of hypoglycemia with its immediate improvement upon the administration of glucose, followed by the signs of pulmonary involvement complicated the picture and made surgical intervention inadvisable. It was not until after the autopsy that the entire clinical picture was understood.

DISCUSSION

These two cases present the classical syndrome of generalized peritonitis secondary to spontaneous rupture of a pyosalpinx. There is a history of a sudden abdominal calamity starting as a sharp abdominal pain associated with persistent vomiting. On admission to the hospital, signs of severe shock, with evidences of an "acute abdomen" are found. Both patients present marked abdominal rigidity, tenderness, and rebound tenderness. In addition, vaginal examination reveals evidence of an old pelvic infection. There are a leucocytosis and an increased sedimentation rate in both cases, as well as a preterminal rise in temperature.

SUMMARY

1. The history of generalized peritonitis secondary to ruptured pyosalpinx is briefly reviewed.
2. Although not a common complication of gonorrhea in the female, rupture of a pyosalpinx accounts for 8 per cent of all cases of generalized peritonitis.
3. In the majority of cases of spontaneous rupture of a pyosalpinx, there is no assignable cause for the perforation. There is no strict correlation between perforation and the number of acute attacks of salpingitis or the size of the pyosalpinx.
4. The diagnostic features consist of a sudden onset of a diffuse and rapidly spreading peritonitis associated with a state of circulatory collapse, followed by a rapidly rising temperature, a leucocytosis and an elevated erythrocyte sedimentation rate.
5. The treatment of choice of this condition is a bilateral salpingectomy followed by the insertion of a Mickulicz' or tube drain into the pelvis.
6. The prognosis depends upon the general state of the patient, the time of surgical intervention, the nature of the operation instituted, and to a lesser extent, the bacteria present at the time of perforation.
7. Two cases of generalized peritonitis secondary to spontaneous rupture of a pyosalpinx are here presented and discussed.

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TUBERCULOSIS OF THE CERVIX

WITH REPORT OF A SO-CALLED PRIMARY CASE

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THE purpose of this paper is to report 18 cases of tuberculous cervicitis, one of which is definitely primary in the genital tract, and apparently the only active lesion in the patient. Tuberculosis of the cervix is very rare and is of interest because it clinically may resemble carcinoma of the cervix, and, if secondary to other genital or extra-genital tuberculosis, announces the presence of the infection. If it is the only tuberculous lesion in the genital tract it may indicate tuberculous epididymitis in the marital partner.

In 1919 Moore³³ stated that there were probably not more than 20 undoubted cases of primary tuberculous cervicitis, and in the tabular summary of Counsellor and Collins¹¹ in 1935 this number was reduced to 11. Further study on two of these has shown them to be secondary and thus only 9 true cases remain. The reason for the decrease in number of cases is the increasing exactness of definition accorded the term "primary." In some instances the infection is the first or only tuberculosis in the genital tract, and many authors have reported primary cases on this basis. The most recent writers interpret the term as meaning the primary lesion in the patient, which allows its etiology to be exogenous only. This is as it should be, for the term "primary," when used in connection with tuberculosis, should refer only to the classical early or primary lesion occurring in the lung. Thus an old inactive pulmonary scar must count as the primary lesion, even though the cervix contains the only active focus of tuberculous infection. Since a large percentage of our population is early infected with pulmonary tuberculosis, the occurrence of a true primary tuberculous cervicitis is an improbability. The author wishes to report his case as one of tuberculosis of the cervix, with this being the only focus of this infection in the genital tract.

* * * * *

The history of tuberculosis of the cervix can be traced through the papers of Reynaud,³⁹ who reported the first case in 1831, Boivin and Dugés,⁶ Geil,²⁰ Virchow,⁴⁵ Rigal,⁴⁰ Cohnheim,¹⁰ and Babes.¹ More recently the literature on this disease has been summarized by Beyca,⁴ Murphy,³⁴ Moore,³³ Greenberg,²¹ Counsellor and Collins,¹¹ and, in 1936, by Finlayson.¹⁹

In the Department of Pathology of the Johns Hopkins Hospital and Medical School, 0.9 per cent of all autopsies on women have shown genital tuberculosis.

From the literature we find that from 5 (49) to 12 per cent (31) of the women dying of tuberculosis have involvement of the genital tract. The cervix is said to be involved in from 3.5 (22) to 8 per cent (47) of the cases of genital tract tuberculosis. Because of the almost universal practice of supracervical hysterectomy in pelvic inflammatory disease Jameson (of Saranac)²⁶ feels that these figures on the frequency of occurrence of tuberculous cervicitis are probably too low. There have been 18 recognized cases of tuberculosis of the cervix in the Gynecological Pathology Laboratory of the Johns Hopkins Hospital, one of which is, as far as we can determine, the sole lesion in the genital tract. These have been found in the 307 cases of genital tract tuberculosis in our laboratory, thus establishing an incidence of 6 per cent for cervical involvement in this genital tract disease. In Greenberg's paper from our laboratory²¹ two cases which were reported as apparent "primary" tuberculosis of the cervix have since been found, through further study, to be secondary to upper genital tract tuberculosis.

Finlayson¹⁹ reviewed the work on experimental implantation of tubercle bacilli in the lower genital tract of animals and concluded that the cervix does not usually become infected unless there is trauma or previous inflammation with erosion. As the result of vaginal inoculations in sensitized guinea pigs, Jameson²⁷ has concluded (1) that a break in the mucosa is not necessary for infection, (2) that the bacilli probably penetrate it through the interstices of the epithelial cells, (3) that they then establish themselves in the submucosa and spread through it by lymphatic extension, and (4) later ulcerate back through the epithelium into the vaginal cavity.

Cohnheim¹⁰ suggested coitus with a male with genital tuberculosis as a cause of primary genital tract tuberculosis in the female, but tubercle bacilli have apparently never been demonstrated in the semen of living human beings. There has been no undoubted so-called "primary" cervical tuberculous infection reported in a virgin, all definite ones having occurred in married parous women or in those given to sexual excesses. Finlayson, Chaton, and Bender have described cases where the infection arose shortly after parturition. Finlayson reports four cases in which tuberculosis of the vulva or vagina occurred simultaneously with cervical tuberculosis, and he believes that the cervix was the primary site in one of them. Jameson²⁸ states that upper genital tract tuberculous infections generally are descending ones and very rarely extend below the internal os, while lower tract infections are ascending and practically never extend above it.

In computing the averages from many figures in the literature one finds that about 95 per cent of the cases of tuberculosis of the cervix are secondary to active tuberculosis elsewhere in the body, and that approximately 85 per cent of cervical tuberculosis is secondary to upper genital tract infection. Thus about 10 per cent of the cases of this cervical infection are secondary to tuberculosis of the gastrointestinal, pulmonary, or skeletal systems, the bacilli being presumably blood-borne from these foci to the cervix. We also find that the Fallopian tubes are infected in about 90 per cent of all genital tract tuberculosis, the endometrium in about 75 per cent, the ovaries (usually on the surface) in 30 per cent, the cervix in 5 to 6 per cent, and the vagina and vulva in 0.5 per cent.

The pathologic process in the cervix may be superficial, but more often it is deep, and it spreads along the course of the blood vessels apparently by way of the lymphatics (see Figs. 1 to 4). The cervical

glands show hyperplasia and hypersecretion, and are rarely engulfed by the process. Spread from the cervix is said to be by direct extension,¹⁹ the vaginal fornices being first affected, the endometrium next, and shortly thereafter the broad ligaments. The spread from the cervix seems to be slow, and in the author's "primary" case it had not taken place six months after the apparent onset of symptoms. There is no evidence which conclusively shows that remote metastasis ever takes place from cervical tuberculosis. The process in the cervix takes four general forms. The *papillary or vegetative* and the *ulcerative* types are the two most commonly seen, and derive their names from the gross appearance of the cervix. The *interstitial* type is more rare and the infection is deep-seated from the first, apparently being blood-borne from a bodily focus. The *endocervical or catarrhal* type is the earliest form and can be diagnosed only by biopsy as the cervix may show only slight peri-oral erosion or eversion.

Cervical tuberculosis is most frequently mistaken for carcinoma. This fact may account for some of the so-called cancer cures following amputation of the cervix where there was a vegetative growth present and no microscopic examination was made. It is next most often mistaken for the various venereal ulcers and papillary growths, and may be confused with localized gland hyperplasias, traumatic lesions, erosions, mucous polypi, sarcoma, actinomycosis, and simple hypertrophy.⁴⁶ An absolutely positive diagnosis is made only with a biopsy in which the stained bacilli can be demonstrated. In an early case a fragment of excised tissue carefully ground up in a small amount of normal saline and injected into a guinea pig may give a positive diagnosis (if the stained guinea pig gland smear shows the bacilli) where microscopic studies have failed to do so.

The disease occurs most frequently in the 20 to 40 year age group, and its racial predilection is for the American negress. The symptoms are persistent offensive leucorrhea, slight postcoital bleeding, dull pelvilinear pain, and the menses may be or have been normal-to-profuse or scanty-to-absent, generally indicating fresh uterine involvement or general systemic and extensive genital tract involvement, respectively. It is interesting to note that the first three symptoms listed above are the cardinal ones of cervical carcinoma as well, and would naturally lead the examiner to suspect it before tuberculosis. Physical examination reveals a bulky, firm, slightly friable, often non-tender, fairly easily bleeding cervix. It usually shows the papillary or ulcerative forms, and, if advanced, there may be vaginal fornical induration. Some differential diagnostic points which might help to distinguish it from carcinoma are that it is usually more injected, less friable, of more even and moderately firm consistency and the hypertrophy is almost always more symmetrical.

Beyea, Murphy, Moore, Brook, Spalding, Harris, Bishop, and Neu all agree that the treatment should be surgical when possible and as radical as the condition of the patient will allow. Involvement of the bladder or rectum, marked genital tract tuberculosis with involvement of adjacent tissues, active tuberculosis elsewhere

in the body, and the usual heart and pulmonary diseases are contraindications to operation. Cauterization alone is insufficient and inadvisable as it may spread the infection.^{35, 36} Ultraviolet light and general sanatorium regime have helped inoperable cases, and may build them up to a point where operation is possible. Many cases of secondary and a few "primary" tuberculous infections of the cervix have had apparent complete cure following panhysterectomy and bilateral salpingectomy, with removal of ovaries where indicated. This is the operation of choice as soon as the biopsy diagnosis is made.

* * * * *

Eighteen cases of tuberculosis of the cervix (Gyn. Path. 546, 714, 1847, 2792, 12632, 13607, 14666, 20640, 20840, 23238, 24197, 29471, 30623, 34106, 34554, 35997, 41446, and 44043)* have accumulated in the Gynecological Pathology Laboratory of the Johns Hopkins Hospital during the forty-seven years of its existence. Of these cases 13, or 72 per cent, were in negro women, and the average age at which the infection was discovered was 23.2 years. All of the women had complained of leucorrhea, 11 had had postcoital bleeding, 13 had had amenorrhea, and 3 had had metrorrhagia. A history of personal or familial tuberculosis was obtained in 8 of the cases, while 6 of the patients had shown some clinical evidence, quiescent or active, of pulmonary tuberculosis. The treatment in 14 of the cases consisted of panhysterectomy and bilateral salpingo-oophorectomy, and roughly 3 out of 4 are alive and apparently well. One of the cases had advanced pangenital tuberculosis when first seen and was given ultraviolet light treatments and put on a sanatorium regime. She is alive and fairly well despite the fact that her pelvic organs are solidly fixed and she has chronic constipation. The other 3 patients were practically moribund when seen and only a cervical biopsy was taken. Autopsy studies on two of these showed the presence of advanced genital and pelvic tuberculosis. From the 17 patients in whom it was possible to obtain operative and autopsy specimens tuberculous salpingitis was found to have an incidence of 87 per cent.† Tuberculosis was found in the endometrium in 84 per cent of the cases, in the ovaries in 39 per cent, and in the myometrium in 22 per cent. In one case the cervix contained the only tuberculosis found in the genital tract.

The microscopic picture was essentially the same in every case. There was usually some degree of superficial glandular hyperplasia with a few tubercles in the mucosal stroma. The stroma was always relatively densely infiltrated with lymphocytes (see Fig. 1), and in some cases germinal nests of these cells were found. The more easily recognizable were the larger tubercles which, with their giant cells, were situated deep in the body of the cervix and in practically every instance lay near an artery and snugly up against a lymph vessel (see Figs. 2 and 4). One tubercle in Fig. 4 appears as though it opens into the adjacent lymph channel. The presence of these large tubercles

*One of these cases has been reported,¹⁴ and seven were mentioned.²¹

†In some cases where the endometrium was biopsied the tubes were not removed because the patient refused to have a laparotomy. Thus the figure for the incidence of tuberculous salpingitis is probably low.

deep in the body of the cervix and their nearly constant perilymphatic locations are the two most striking findings in the histologic picture of the disease.

* * * * *

The following is the report of a case in which the cervical tuberculosis was apparently the only active lesion in the patient and definitely the only one in the genital tract.

A. C. (Unit No. 74028), a 24-year-old married negress and the mother of two children, first came to the Gynecological Dispensary of the Johns Hopkins Hospital on Sept. 28, 1936. Her chief complaint was lower abdominal cramplike pain for two or three days following apparent cessation of her menstrual periods. This began six months before she was seen, became progressively more severe, and the last attack (September 19 to 21) brought her to the hospital. She had had pain since the end of her last period, but it was relieved when she bled profusely the



Fig. 1.—(Gyn. Path. 44043.) The original cervical biopsy. Note the proliferation of the glands into localized gland nests, the dense lymphocytic infiltration of the stroma, the giant cell with coronal arrangement of the nuclei (A), and the eroded surface epithelium (B). (This tissue was taken from the everted granulation tissue around the os.) ($\times 70$.)

night before she was seen. She had had a moderate leucorrhea for five years, but it had been more profuse following the birth of her youngest child two years before coming to the hospital. For the last four months this discharge had been watery and foul. She had had burning on urination for the two weeks prior to coming to the hospital. None of her family had had recognized tuberculosis. Her general health had been good although she had always been thin and underweight. She had had two full-term normal spontaneous deliveries. A biopsy of the cervix showed some tuberculosis (Fig. 1), and she was admitted to the hospital.

Physical examination showed the following: temperature 99.6° F., pulse 80, respirations 20, blood pressure 140/80, hemoglobin 86 per cent, leucocyte count 15,500, weight 92 pounds; the white blood cell differential count was normal, a catheterized specimen of urine was negative chemically and microscopically, and the blood Wassermann test was negative. She was definitely undernourished. The superficial glands and breasts were negative. The heart and lungs were normal to percussion and auscultation but a chest x-ray showed very slight thickening of the

pleura at the right costophrenic angle. The abdomen was thin-walled, scaphoid, and negative. The pelvic examination disclosed negative Bartholinian glands, a parous outlet, and there was a profuse mucopurulent white discharge of thinner consistency than normal. The cervix was about three times normal size, of relatively normal contour, and of an even but firm consistency. It was freely movable, nontender, and there were superficial lateral lacerations which were made prominent by the marked eversion and hypertrophy of the anterior and posterior lips. The everted portions were injected and granular but not very friable, and the examination caused only slight bleeding from them (see Fig. 5). The external os appeared to be firmly closed by the redundant lips and was marked by a slight horizontal linear

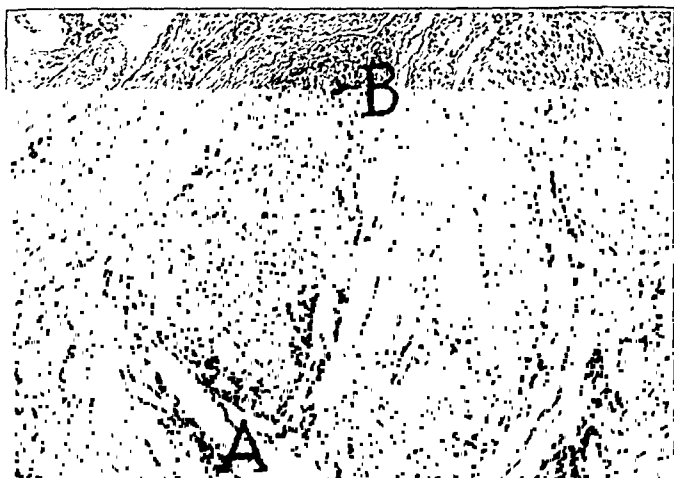


Fig. 2.—(Gyn. Path. 44112.) A large tubercle situated between several blood vessels deep in the body of the cervix. The tubercle apparently lies in the wall of a lymph vessel (A). Note the giant cell at the edge of the tubercle (B). ($\times 70$.)



Fig. 3.—(Gyn. Path. 44112.) A section through the portio of the anterior lip. The stratified squamous epithelium is intact and the stroma immediately beneath it shows only a physiologically normal amount of lymphocytes. Note the tubercle with giant cells situated in otherwise normal stroma a short distance beneath the surface. ($\times 60$.)

indentation. There was no induration of the vaginal vault or the parametrium. The uterus was normal in size, shape, consistency, and motility, and was in mid-to anterior position. There were no pelvic masses or tenderness, and the ovaries were small and free. The rectal examination was negative and confirmed the pelvic examination. There were no other positive findings.

A panhysterectomy and bilateral salpingectomy were done. The ovaries were normal in appearance and were entirely free from adhesions so they were not removed. She withstood the operation well, the lower abdominal incision healed per

studied. We understand the function of the interstitial cells in the male, because if the testicle is undescended, the tubules degenerate, but there is no comparable situation in the ovaries.

There is considerable dispute about the origin of the male interstitial cells. Do they arise from the connective tissue or from certain of the genital cells not included in the cell cords which go to make up the testicular tubules?

The genitaloid cells at certain periods seem to stand out distinctly in the mass of the testis. They are to be found in the embryonic male gonad and also after the age of puberty but, according to the best authorities, between birth and the age of puberty they are not to be found. What happens to them in this interlude? Do they disappear or disguise themselves and then reappear at puberty? If they degenerate in embryonic life, what then is the cause of their reappearance at puberty? These genital cells, about which we can say very little except that they have a characteristic appearance, are to be seen in the rete blastema up to 55 mm. in length in the male, and they then disappear and the rete goes on to form cords. If these cells in the main body of the testis can disappear at birth and reappear at puberty, why can they not do the same in the rete? Yet, if they are an entirely new development instead of a reappearance of disguised cells, their significance in the male would be just as obscure as in the female.

After all the rete ovarii is apparently a normal structure present in every ovary. It is vestigial, but so is the epoophoron. These structures are always to be found and their presence casts no doubt, of course, on the female nature of the individual bearing them. Since they have an origin which is analogous to the origin of the cells in the male, perhaps they are the homologue of the interstitial cells in the male. They belong there and the ordinarily spoken of ovarian interstitial cells are something else with a different function.

DR. SIDNEY DUNNE.—Considerable work by Koch and many other workers has been carried out in male hormone assays in men and women, both normal and those with certain pathologic conditions associated with virilism. Results in this work vary considerably. According to Koch, it is impossible at this time to support the theory that virilism is due to a hypersecretion of a recognized comb-growth stimulating hormone. While it has been proved that the gonads are the main source of male and female sex hormones, yet in castrated men and women such hormones can be detected in the urine. Moreover, in cases of virilism due to adrenal tumors, the tumor itself, as Dr. McCahey has shown, has failed in some instances to contain an excess amount of male hormone. Thus, until we know more about the chemistry of male and female sex hormones no definite conclusions can be shown with regard to the source or role of the androgenic hormone in virilism.

With regard to the arrhenoblastoma, or masculine-like tumor of the ovary, very few cases have been reported in this country. Baldwin and Gafford have collected all the cases in the literature up to 1935 and found 34, including their own. A few cases have been reported since their paper. No male hormone assays have been carried out in these cases to allow any discussion on this point. The interesting fact connected with this tumor, as Dr. McCahey has shown, is that the most differentiated type shows no, or very slight, masculinizing effect while the type which resembles testicular tissue most is always accompanied by marked virilism.

DR. CHARLES MAZER.—An excess of male sex hormone (testosterone) said to be present in the urine of patients suffering from arrhenoblastoma, does not prove that the excess of the hormone is directly responsible for the syndrome of virilism. Reproduction of the syndrome by the administration of testosterone would prove the point. I have found, however, that the administration of $2\frac{1}{2}$ to 25 mg. of testosterone every other day for a period of months, for the purpose of arresting benign menopausal uterine bleeding, does not produce virilism. Its effect is apparently limited to the generative organs wherein it produces hypoplasia and arrest of the benign uterine bleeding.

I want to stress the inadequacy of our present method of determining the quantity of male sex hormone in the urine of patients showing a tendency to masculinity. The "comb unit" is so large that one can employ only two or three

Microscopic examination of the cervix (Gyn. Path. No. 44043, No. 44112) revealed a picture essentially similar to that general one described above in the paragraph just preceding this case report. The histopathology of the tuberculosis in this cervix is essentially pictured in Figs. 1 to 4.

The cervical canal was lined with a shallow layer of mucosa in which, although the glands were normal, the stroma was densely infiltrated with lymphocytes. A careful search disclosed no tubercles in the canal. Many sections through the uterus disclosed normal myometrium, and the endometrium was slightly infiltrated with lymphocytes and showed a normal nonsecretory interval phase. Half a dozen sections from each tube showed small lumina, delicate and discrete mucosal folds, no inflammatory cells, and a normal thin serosa. Acid-fast stains on all sections from the cervix showed no tubercle bacilli after careful search. The pathologic diagnosis was tuberculous cervicitis; interval endometrium, nonsecretory; normal myometrium; normal Fallopian tube bilateral.

The exact significance of the presence of the large tubercles deep in the cervix in this case cannot be ascertained, but, in view of the apparent absence of any other genital or extragenital active tuberculous focus one might surmise that the infection has penetrated deeply from a superficial mucosal implantation. In addition, the nearly constant perilymphatic location of the tubercles in this case implies that the infection possibly spreads by way of the lymph channels.

It should be remembered that Langhans' giant cells and tubercle-like structures are also found in Boeck's sarcoid,²⁹ in the lesions caused by *B. melitensis*, and in some of the organs removed routinely at autopsy where syphilis was the only known disease before death.

* * * * *

In a few cases, when the patient showed no evidence of tuberculosis outside of the cervix, the exogenous etiology has been demonstrated by the finding of genital tract tuberculosis in a marital partner. As a result of thorough chest and genitourinary studies on the husband of the author's case, no tuberculosis could be found. However there is no guarantee as to the absolute fidelity of the wife, and other partners undoubtedly exist despite her denials.

For those who desire recourse to recently reported "primary" cases the author recommends those of Douglass and Ridlon,¹⁸ White,⁴⁸ Harris,²⁴ Missett,³² and Dannreuther,¹⁵ and for more complete bibliographies and studies of the subject the articles of Bonnet and Bulliard⁷ and Finlayson,¹⁹ and the monographs of Norris³⁶ and Jameson.²⁶

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SUMMARY

1. Eighteen cases of tuberculous cervicitis are reported, one of which is the sole tuberculous focus of infection in the genital tract, and the only active one in the patient.

2. Tuberculous cervicitis is of chief interest because it clinically resembles cervical carcinoma and announces the presence of genital tuberculosis.

3. The cervix is involved in from 5 to 8 per cent of the cases of genital tract tuberculosis and thus appears to have a relative immunity to this infection. About 90 per cent of the cases of cervical

primum, and her postoperative course was remarkably uneventful. She was discharged fifteen days after operation. Since then she has felt well, has developed a good appetite, and when seen in June, 1937 had gained 7 pounds. Repeated chest studies have revealed nothing more than was originally found. The following report on her chest plates was made by Dr. John W. Pierson: "Roentgenological studies of the chest show no active tuberculosis. There has been tuberculous infection in the past but no more than is found in a large percentage of Baltimore negroes."



Fig. 4.—(Gyn. Path. 44112.) A section from deep in the body of the cervix. One of the tubercles half surrounds a lymphatic, and looks as though it has ruptured into it (A). ($\times 70$.)

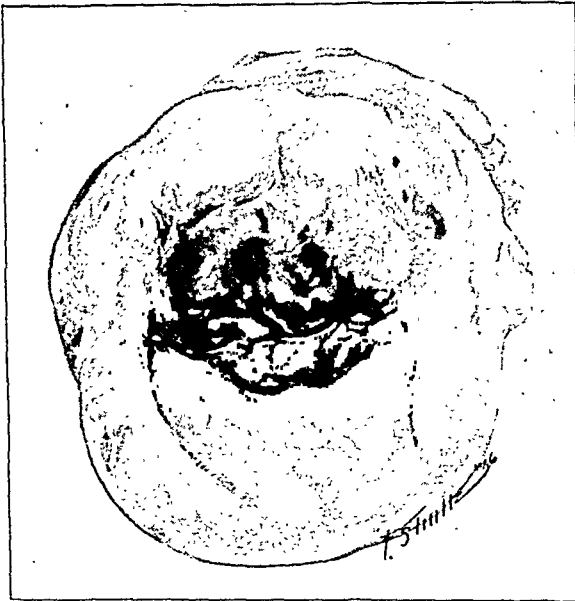


Fig. 5.—Appearance of cervix when first seen. Drawing slightly less than actual size.

The gross pathologic examination of the operative specimen showed the hypertrophied cervix, as described above, the external os of which would admit only a small probe. After fixing in formalin, which causes slight shrinkage, the cervix measured 5 cm. in diameter. The portio was intact save for a border of erosion and ulceration 1 cm. wide around the external os. The consistency was firm, being that of dense fibrous tissue, and on section there was slight injection of the stroma beneath the ulcerated portion of the portio. The surfaces of the uterus and tubes were smooth and shiny, and these organs were grossly normal in every respect.

THE QUANTITATIVE DETERMINATION OF ESTROGENIC SUBSTANCES IN NORMAL FEMALE URINE THROUGH THE INCEPTION OF A PREGNANCY*

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IN A PREVIOUS paper¹ we have reported the results of quantitative determinations of estrogenic substances in normal female urines during the menstrual cycle, with details of extraction, the injection of the extracts and the biologic assay. These determinations were done on successive twenty-four-hour specimens of urine, which were collected in some instances to include one complete cycle, and in others more than one, a few consecutive and a few not.

The graphs obtained showed two principal peaks during the cycle, the first of which we believe to represent the height of follicle activity just before rupture, and the second the height of corpus luteum development and activity. The second peak is always followed in normal cases by a rather rapid drop to zero, which in turn is followed in varying short periods of time by menstruation.

The graph shown here (Chart 1) was obtained in the course of an estrin excretion study of a normal individual in whom pregnancy occurred during the time comprised by the study. She was 18 years of age. General and gynecologic examinations were entirely negative. There had been one pregnancy two years before, which had been normal, with normal delivery and puerperium. The menstrual history had always been normal, with approximate twenty-eight-day intervals.

As shown in the graph, urine specimens were obtained beginning ten days before a menstrual period. They were collected daily through the ensuing menstruation and continued through the following interval. The next expected menstrual period did not occur. Specimens were collected for a few days more and discontinued. The date of the last menstrual period was Feb. 4, 1936, and she was delivered by one of us (L.W.M.) on Nov. 10, 1936. The entire course of the pregnancy was normal.

Preceding the last menstruation, there is a peak of estrin excretion at *CL*, followed by a rapid fall and menstruation twenty-four hours later. This premenstrual curve is characteristic of all those we have obtained on normal individuals. Following menstruation there are several relatively slight rises in estrin excretion, with disappearance on one or more days, the significance of which we do not know. We have found this in a number of other cases.

The first appreciable peak reached in the curves obtained in all of our other cases is in the relative position of the one marked *O* on Chart 1. As stated above and previously, we believe this to represent the height of follicle activity just prior to rupture. As can be seen by referring to our previous paper, they have all been considerably higher than in this case. Otherwise the pictures are fundamentally the same.

*This investigation was aided in part, by a grant from the National Research Council, Committee on Problems of Sex.

tuberculosis are secondary to upper genital tract infection. A true primary cervical tuberculosis is extremely rare.

4. The two chief symptoms are a persistent offensive watery leucorrhea, and bleeding following coitus or douching.

5. Physically the cervix shows symmetrical hypertrophy and superficial friability and the portio may show abnormalities ranging from erosion and eversion to ulceration or papillary granulations.

6. The treatment should be surgical when possible and as radical as necessary and as the condition of the patient will allow.

7. The microscopic pathology is treated in detail and is chiefly characterized by large tubercles lying snugly up against lymphatic channels deep in the body of the cervix and Langhans' giant cells and tubercles scattered through hyperplastic canal mucosa.

8. The term "primary tuberculous cervicitis" demands that it be the only tuberculous lesion in the patient.

The author wishes to thank Dr. Thomas S. Cullen and Dr. Arnold Rich for their help and advice in the preparation of this paper.

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much as 700 or more international rat unit equivalents in one twenty-four-hour specimen, while the specimen for the preceding twenty-four hours, and the one for the following twenty-four hours, contained none. It is evident that were the specimens obtained even three times a week, if none were examined for that particular twenty-four hours, one might erroneously conclude that there had been no estrin excretion in the interim.

It is to be hoped that an increasing number of similar graphs can be accumulated for study, but it can be appreciated that to secure one will always be pretty much of a fortunate accidental occurrence. The values of such graphs, particularly in sterility studies, and in connection with the subject of contraception, is evident.

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HYSTERECTOMY

A TEN AND A HALF YEARS' STUDY

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WE HAVE made a study of all the hysterectomies performed in Multnomah Hospital in a period of ten and a half years, from July, 1925 to January, 1937. During that time 779 hysterectomies were performed. There were 20 deaths, an incidence of 2.56 per cent. Each case in this survey was carefully considered from the standpoint of age, complaints, preoperative diagnosis, type of hysterectomy, complications, operative and postoperative progress, pathologic findings, and mortality.

PREOPERATIVE CONSIDERATION OF PATIENTS

We have tabulated only the five principal complaints (Table I). There were, of course, many others. It will be noted that almost all of the patients complained of pain and discomfort, over half complained of abnormal vaginal bleeding, and fully one-fourth complained of urinary disturbances of some kind or other. A number of tumors were found in routine examination.

There were 17 patients in the group of ages up to and including 19 years, and 111 in the group from 20 to 30 years. Ninety-six patients were between 50 and 60 years old, and 43 were 60 years and over. The ages of the remaining 512 patients (65.72 per cent) ranged from 30 to and including 50 years.

The preoperative diagnoses (Table II) can be covered almost entirely by three conditions; namely, tumors, uterine prolapse with its accompanying cystocele and rectocele, and pelvic inflammatory disease. Tumors alone accounted for practically three-fourths of the preoperative diagnoses, while 185 patients suffered from the sequelae of pelvic inflammatory disease.

As in all other cases, this peak is followed by a fall, in this case to zero (in several other cases to zero, in others not), and the curve in turn rapidly rises to the second peak *CP*, which is in the present instance identical in I.R.U.E. (International rat unit equivalents) with the premenstrual peak *CL* in the previous cycle. This peak we believe represents the height of corpus luteum activity.

As can be seen, there is the usual beginning premenstrual drop, but only to about 480 I.R.U.E., whereupon there is a rapid intermittent rise. This is in line with what we know about the persistence of the corpus luteum of pregnancy. It seems certain that conception occurred somewhere between *O* and *CP*. We believe that the halt to the estrin fall, following the peak *CP*, probably represents nidation of the fertilized ovum, and that the increase in estrin output may either be caused by some stimulus to the corpus luteum by this phenomenon, or it may be directly referable to the very young trophoblast itself. Since we believe that later the entire hormone function is taken over by the placenta, the latter view seems entirely possible.

It is of interest to note that the peak *CL* occurred five days previous to the last menstrual period, and that the peak *CP* also occurred just five days preceding what

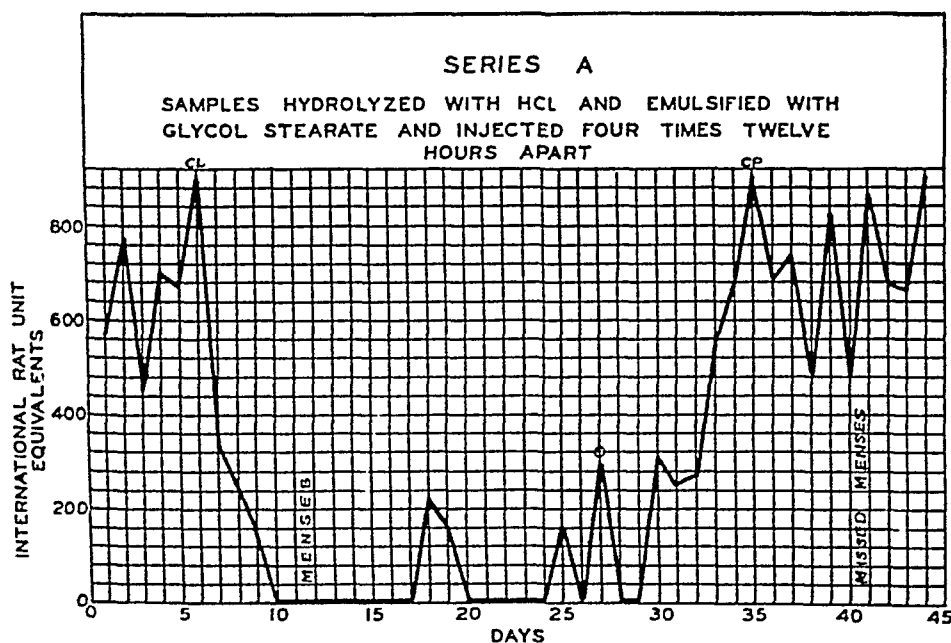


Chart 1.

would have been the next menstrual period in the twenty-eight-day cycle, had it occurred. As stated in our previous paper, however, this equality of time relationships between the estrin peaks and menstruation, or of the peaks to each other, does not necessarily obtain, even in succeeding cycles in the same individual.

Smith and Smith² have reported estrin studies in two cases which covered the periods of ovulation, conception and early gestation. Their studies and ours are fundamentally alike, both for the regular menstrual cycles and during the inception of pregnancy. They differ, however, in that we have consistently found a peak which we believe to represent the height of follicle development before rupture, and also in that we have not found the constant relationship between the corpus luteum peaks and the subsequent menstrual periods. Their extractions were done on twenty-four-hour specimens obtained twice a week or oftener. Koch and his associates³ have made similar studies of normal menstrual cycles and have found a suggestion of two peaks during the cycle.

We are of the opinion that only the analysis of daily specimens gives a true picture of urinary excretion of estrin, since we have found as

(Table IV). Salpingectomy and oophorectomy were performed on more than half of the patients. Many of the hysterectomies, where it seemed expedient, were done in conjunction with bilateral salpingectomy and other surgical procedures.

OPERATIVE AND POSTOPERATIVE PROGRESS

In eight instances the operation was complicated by hemorrhage. Three of the hemorrhages formed hematomas in the broad ligament, and one was the result of rupture at the internal os with a Hegar dilator. In two instances there was an injury to the bladder followed by a vesicovaginal fistula, but in no instance was there an injury to the ureters. Primary shock occurred in six patients. One patient had diabetes, and one had heart disease.

One hundred and fifty-seven patients (20.15 per cent) had postoperative complications of various kinds (Table V). The heading "other complications" in the table includes (one case of each) nephritis with uremia and subsequent death, infected hematoma of the pelvis, hypertension with cardiovascular renal disease and fibrillation, pulmonary infarct, thrombosis of the femoral vein, and unexplained

TABLE V. POSTOPERATIVE COMPLICATIONS

COMPLICATION	NUMBER
Infected incision	43
Cystitis	17
Pelvic abscess	16
Pyelitis	14
Pneumonia	13
Ileus (1 obstruction)	11
Hemorrhage	10
Peritonitis	10
Hernia	7
Fistula (3 abdominal, 2 vesicovaginal, 1 rectovaginal)	6
Evisceration	2
Hematoma	2
Damage to ureters	0
Other complications	6

TABLE VI. MALIGNANCIES FROM PATHOLOGIC REPORTS*

SITE	CASES	TYPE OF MALIGNANCY	OTHER LESIONS
Fundus	23	13 Adenocarcinomas	1 Adenomyoma
			1 Cervicitis
			1 Chronic salpingo-oophoritis
		3 Papillary adenocarcinomas	1 Myoma and pyosalpinx
			1 Fibromyoma
		3 Squamous cell carcinomas	None
		3 Carcinomas (unclassified)	1 Chronic salpingitis
		1 Chorionepithelioma	None
Cervix	6	2 Squamous cell carcinomas	1 Myoma and chocolate cyst
		4 Carcinomas (unclassified)	1 Hydrosalpinx, cystadenoma of ovary
Ovary	8	1 Adenocarcinoma	Peritoneal implantation
		4 Papillary adenocarcinomas	1 Leiomyoma
		1 Primary carcinoma	Fibromyoma and chronic sal- pingitis
		1 Malignant serous cystade- noma	Myoma uteri
		1 Malignant cystoma papillif- erans	None
Tube	1	1 Carcinoma (unclassified)	None
Sigmoid	1	1 Adenocarcinoma	Myoma uteri

*Of late practically all patients with carcinoma of the cervix have been treated with radium.

TABLE I. FIVE PRINCIPAL COMPLAINTS

COMPLAINT	NUMBER	PER CENT
Pain and discomfort	705	90.50
Abnormal vaginal bleeding	475	60.97
Urinary disturbances	183	23.49
Tumors	155	19.89
Leucorrhea	125	16.04

There were, of course, many other complaints. These are the chief complaints as registered on the records.

TABLE II. PREOPERATIVE DIAGNOSIS

DIAGNOSIS	NUMBER
Fibromyoma	339
Relaxed perineum (including cystocele, rectocele, and urethrocele)	241
Pelvic inflammatory disease	185
Prolapse (with cystocele and rectocele)	122
Lacerated cervix (4 with polyps)	97
Ovarian cysts	91
Fibrosis uteri	42
Carcinoma of fundus (1 chorioepithelioma)	27
Retroversion	10
Ectopic pregnancy	10
Carcinoma of cervix	9

OPERATIVE PROCEDURES

The hysterectomies in this series were of the total, subtotal, and vaginal types, with a preponderance of the subtotal (Table III). The vast majority of the patients had additional operative procedures at the time the hysterectomy was performed

TABLE III. TYPE OF HYSTERECTOMY AND MORTALITY

TYPE	NUMBER	DEATHS	PER CENT
1. Subtotal	572	11	1.92
2. Total	79	6	7.59
3. Vaginal	128	3	2.34
Totals	779	20	2.56

TABLE IV. ADDITIONAL PROCEDURES

PROCEDURE	NUMBER
Oophorectomy (219 unilateral, 220 bilateral)	439
Salpingectomy (101 unilateral, 315 bilateral)	416
Perineorrhaphy	223
Appendectomy	152
Diagnostic curettage (12 with biopsy)	86
Anterior colporrhaphy	21
Cautery of cervix	19
Ovarian transplantation	17
Radium	14
X-ray	13
Trachelorrhaphy	13
Herniorrhaphy	6
Miscellaneous	18

The discrepancy between the number of oophorectomies and the number of salpingectomies is explainable by the fact that some of the patients had had their tubes removed at a former operation.

other pathologic conditions existed simultaneously with the malignancies. Three hundred and forty-four patients had fibroid tumors. In only 8 instances (2.32 per cent) was the fibroid associated with malignancy; this association was purely coincidental.

In this series of 779 hysterectomies there were 20 deaths, a mortality of 2.56 per cent. The deaths, considered from the standpoint of individual surgeons, are listed in Table VII. In studying this table, one cannot fail to be impressed by the fact that the mortality rate was constantly in inverse ratio to the number of patients operated upon—the greater the number of operations, the lower the percentage of deaths. Most of the operations were done by attending gynecologists and residents on the gynecologic service. Five attending gynecologists did 653 operations with 18 deaths, and 8 resident gynecologists did 126 operations with 2 deaths, a mortality of 2.75 and 1.58 per cent respectively. The operations by the residents were done on selected patients and under the supervision of an attending gynecologist.

We have also made a study of the statistics of hospitals in which a large number of consecutive hysterectomies were done (Table VIII), and found that the mortality for the three types—subtotal, total, and vaginal—ranged from 0.47 to 14.3 per cent, with an average for each type of 2.74, 3.39, and 1.83 per cent, respectively. We found further that while the same procedure was not favored in all the hospitals, the number of subtotal hysterectomies done far exceeded that of either the total or vaginal types.

The causes of the deaths in our series of cases are given in Table IX. It will be seen that peritonitis was responsible for almost half of them.

TABLE IX. CAUSES OF DEATH

CAUSE	NUMBER
Peritonitis	8
Pneumonia	3
Embolism	3
Shock	3
Hemorrhage	1
Uremia	1
Generalized carcinomatosis	1
Total	20

Because Greenhill's mortality¹⁰⁻¹¹ was eleven times as high when both adnexa were removed as when a simple supracervical hysterectomy was done, we studied our cases with this point in mind. Table X shows our percentages with all types of operation. We can offer no explanation for the difference between Greenhill's figures and ours.

TABLE X. MORTALITY WITH RELATION TO ADNEXAL REMOVAL

OPERATION	NO.	DEATHS	PER CENT
Supravaginal hysterectomy			
Without adnexal removal	181	3	1.65
With partial salpingo-oophorectomy*	227	4	1.76
With bilateral salpingo-oophorectomy	164	4	2.43
Total hysterectomy			
Without adnexal removal	21	2	9.52
With partial salpingo-oophorectomy*	18	1	5.55
With bilateral salpingo-oophorectomy	40	3	7.50
Vaginal hysterectomy	128	3	2.34
Totals	779	20	2.56

*Partial salpingo-oophorectomy as used here indicates all combinations of adnexal removal except bilateral salpingo-oophorectomy.

We feel that we have reduced our mortality by a strict observance of the sedimentation rate. This observance has stood us in fine stead as a criterion for operation on patients with salpingitis. We have avoided operation whenever possible

twenty-six days' fever. The average number of febrile days was 4.7, and the average time spent in the hospital was fifteen days.

Dermoids of the ovaries were found in four patients. In one instance the dermoid occurred with an adenomyoma and a parovarian cystoma. Thirty-nine patients had malignancies of one kind or another (Table VI). More than half of these (58.97 per cent) were in the fundus of the uterus. It is interesting to note that in 13 instances

TABLE VII. SURGEONS, OPERATIONS, MORTALITIES

SURGEON*	HYSTERECTOMIES	DEATHS	PER CENT
A	212	3	1.41
A	209	5	2.39
A	99	4	4.04
A	73	3	4.11
A	60	3	5.00
R	49	1	2.04
14 others (R-V)	77	1	1.29
Totals 20	779	20	2.56

*A, Attending gynecologist. R, Resident gynecologist. V, Visiting surgeon.

TABLE VIII. HYSTERECTOMY MORTALITY (VARIOUS HOSPITALS)

HOSPITALS	YEARS	HYSTERECTOMIES								
		SUBTOTAL ABDOMINAL			TOTAL ABDOMINAL			VAGINAL		
		NO. OF CASES	NO. OF DEATHS	PER CENT	NO. OF CASES	NO. OF DEATHS	PER CENT	NO. OF CASES	NO. OF DEATHS	PER CENT
Lane Hospital, San Francisco ¹	10	265	8	3.0	307	10	3.2	73	0	0
San Francisco Hospital ¹	10	408	12	2.9	196	8	4.0	28	4	14.3
University Hospitals, Iowa City ²	7½	274	10	3.6	314	17	5.4	151	3	2.0
Lakeside Hospital, Cleveland ³	13	609	27	4.4	1,078	45	4.1	164	6	3.6
Lakeside Hospital, Cleveland ⁴	5	653	16	2.3	821	22	2.6	70	3	2.9
Mayo Clinic, Rochester ⁵	3	487	9	1.9	1,118	15	1.3	333	7	2.1
Harper Hospital, Detroit ⁶	5	1,141	30	2.6	235	15	6.4	-	-	-
Presbyterian Hospital, Chicago ⁷	-	-	-	-	-	-	-	627	3	0.47
Free Hospital for Women, Brookline ⁸	26	1,900	34	1.7	-	-	-	-	-	-
University of California Hospital, San Francisco ⁹	9½	514	4	0.77	163	1	0.61	70	1	1.4
Cook County Hospital, Chicago ¹⁰	5	1,408	65	4.6	551	26	4.7	158	3	1.9
Multnomah Hospital, Portland	10½	572	11	1.92	79	6	7.59	128	3	2.34
Totals		8,231	226	2.74	4,862	165	3.39	1,802	33	1.83

In the Los Angeles County Hospital¹¹ the types of hysterectomy were not tabulated. In a period of 6 years 2,352 hysterectomies were performed with 83 deaths, a mortality of 3.5 per cent.

In the Cook County Hospital¹² during a period of ten years 3,129 supravaginal hysterectomies were performed for myomas of the uterus. There were 78 deaths, an incidence of 2.1 per cent.

capons in a given test. Animals are known to vary greatly in their response to hormone injections. Some are highly sensitive; others are not. It is, therefore, necessary to employ 12 to 15 animals in a given test to be accurate.

DR. CHARLES WILLIAM DUNN.—Dr. Ramsay's findings clearly indicate the actual and potential bisexual character of the ovary which is very important from an endocrinologic viewpoint. Grollman and others consider the rete ovarii as androgenic tissue. Therefore, this tissue biologically corresponds to the androgenic zone of the adrenal cortex, the adrenal cortical tests, and the accessory adrenal cortical masses. Besides an embryologic, histologic, biologic, and chemical correlation, we find that pathologic lesions of androgenic tissues present a marked clinical similarity. This is prominently exemplified by the Cushing syndrome.

My first illustration is that of a female, aged 62 years, with arrhenoblastoma of the ovary. The virilism, hirsutism, hypertension, and the regional type of obesity is that observed in the Cushing Syndrome, whether it be due to pathology of the anterior pituitary basophile cells and the associated adrenocortical pathology or to carcinoma of the adrenal cortex or the thymus gland. This patient also had a hypertrophied clitoris. This abnormality is more frequently found in virilism and the adrenogenital syndrome.

Broster of England has shown that in most cases of adrenogenital syndrome a marked hypoplasia of the uterus and ovaries is present and is clinically exhibited by amenorrhea or diminished menses and subjective signs of the hypoovarian state. A similar genital pathology and dystrophy exist in the Cushing syndrome, thus we may have in pituitary basophilism or Cushing syndrome, amenorrhea and an abnormal contour corresponding to that of pregnancy.

Pregnancy produces a physiologic hyperplasia of the anterior pituitary lobe, the adrenal cortex, and the thyroid internal secretory cells. If the endocrine hyperplasia regresses to normal after delivery no untoward signs develop; however, if the hyperplasia persists endocrine disorders of the above type may appear.

In a series of 11 patients whom I have diagnosed clinically as Cushing syndrome, there were 9 married and 2 single females. I obtained a history of the onset of this syndrome directly following pregnancy in 5 of the 9 married women. In cases of virilism and adrenogenital syndrome, I also found that pregnancy quite frequently preceded the onset of symptoms. The tendency to virilism at the menopause again illustrates the potential androgenic nature and the bisexual character of the female.

As to the etiology of virilism, Broster reports the isolation by Marrion and Butler (Toronto) of a new chemical which is an androgen and different in character from those previously isolated. This androgen has only been present in cases of the adrenogenital syndrome, and it disappears or diminishes following unilateral adrenalectomy. This substance has not been previously found in the urine of either sex or in pregnancy urine. The chemical formula of this substance is $C_{21}H_{30}O_2$.

Adrenal hypercortical disorders are not always associated with obesity as is evidenced by the leanness of this girl of 9 years of age with a hypertrophied clitoris. Another significant clinical feature in this case is the marked tendency to extensive spontaneous purpura. We also know of the precocious onset of menses in adrenal hypercortical disorders and the early history of excessive menstrual bleeding occurring in many of the cases. This factor of excessive bleeding or disturbed coagulation of the blood might explain the unusually severe metrorrhagia of the case of virilism reported this evening by Dr. Rheuby.

The next case is that of an adult female, aged 29 years. The emaciation was extreme and strikingly simulated that of Simmond's disease. However, the marked hypertrichosis, the hypertrophied clitoris, primary amenorrhea, and abnormal hyperplasia and dysplasia of the internal genitals, differentiate it from Simmond's disease.

Dr. McCahey suggests a very rational surgical procedure in proposing excision of the site of the rete ovarii in cases of virilism and adrenogenital syndrome. It is well known that many of these patients do not respond to unilateral adrenalectomy, therefore it is quite possible that as long as rete ovarii remain in the ovaries suf-

as long as the sedimentation rate remained high. During the last few years we have also avoided doing a hysterectomy on any patient who had had the cervix cauterized a short time before. One death, we found, was caused by an embolus cast off from a thrombus in a vessel in a cauterized area.

More thorough study of each patient, a better selection of the type of operation, more frequent use of blood transfusions, and more experienced surgeons are the important factors in the reduction of the mortality of hysterectomy.

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A COMPARATIVE STUDY OF THE CLASSICAL AND CERVICAL CESAREAN SECTIONS AT THE BROOKLYN HOSPITAL IN A SERIES OF 164 CASES*

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THIS study was suggested when I recently read an article by Frank W. Lynch¹ who had made a comprehensive survey of cesarean sections throughout the United States. He makes the following comment: "It appears as if this operation (meaning the low cervical cesarean section) was almost unknown or not acceptable to the vast majority of physicians who are performing cesarean sections, because, from 60 to 80 per cent of all cesarean sections in the mortality studies were of the classical type."

It is generally accepted by most obstetricians that a low cervical section rather than a classical operation is the procedure of choice when there is any question of infection present. However, there are many who do not feel that the low section should take preference over the classical operation in elective cases.

This paper presents a comparative review of the low and classical cesareans done at the Brooklyn Hospital during the past ten years and certain views which seem to me sufficient reason to advocate the low section in practically all cases. Among the exceptions might be included cases which present mechanical difficulties such as fibroma on the anterior surface of the lower uterine segment, dense adhesions in this region and, possibly those cases where the length of operating time is a factor, especially if the operator is not thoroughly familiar with this type of operation. It is obvious that a comparison should be made, not only of the immediate, but also of the remote results, of both opera-

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tions. Ideally to judge the advantages of one type of operation over the other, a comparison should be made of a large series of cases preferably done in the same hospital where the same operative technique and post-operative care are followed.

While there is evidence that the classical operation continues to be the operation of choice by some in elective sections, it is quite certain that the low cervical section is almost invariably done when there is any question of infection. It is generally felt that the immediate outcome, namely the morbidity and mortality, is definitely lowered by the low operation. Also, we must consider the more remote possibilities, such as a high suspension or fixation of the uterus, the development of adhesions predisposing to intestinal obstruction and the dangerous chance of a rupture of the uterus in a subsequent pregnancy. These all must be taken into consideration when making a decision as to which type of operation should be done, for probably all of the immediate and remote complications are less with a low section.

At the Brooklyn Hospital, covering a period of ten years from 1927 to 1936 inclusive, there were 10,101 deliveries at or near term, 164 of which resulted in a cesarean section, an incidence of 1 in 61. There were 113 classical and 51 low cervical sections.

This series may be too small from which to make any significant deductions but it makes another addition to those already reported on this subject.

TABLE I. INDICATIONS FOR SECTION

	CLASSICAL (113 CASES)	LOW CERVICAL (51 CASES)		CLASSICAL (113 CASES)	LOW CERVICAL (51 CASES)
Disproportion	36	20	Miscellaneous:		
Previous section	32	12	Malpresentation and	8	0
Ruptured uteri	3	0	malposition		
Placenta previa	1	1	Fibromas	6	0
Premature separation	1	0	Cervical dystocia	3	5
of placenta			Previous pelvic	3	2
Heart lesions	8	7	plastic operations		
Toxemias:			Previous myomectomy	1	0
Pre-eclampsia	4	2	Patient who had 5	1	1
Eclampsia	1	0	premature labors		
Chronic nephritis	3	1	with stillbirths		
Unclassified	2	0			

It is worth noting that the three sections done for ruptured uteri all occurred in patients who had been previously subjected to classical sections, none in those who had had low cervical sections. Two of these patients had rather prolonged febrile reactions post partum with the original operation, the third patient also had a moderately febrile post-partum course. This experience is in accordance with most observers who agree that infection following a section favors a rupture during a following pregnancy or labor.

Other procedures that were done in conjunction with the sections are as follows: 32 Pomeroy sterilizations, 1 oophorectomy, 2 myomectomies, and a removal of a fibroma of the abdominal wall.

Two accidents occurred during the operative procedures while doing a cervical section, one was an injury to the bladder and the other was uncontrollable bleeding from the veins of one of the broad ligaments which necessitated a hysterectomy. Both of these patients recovered.

Two ventral hernias developed after the classical operations and two following the low cervical operation.

Operations for intestinal obstruction due to bands which were probably the result of previous classical sections were done on two patients, one a year following the section and the other during the next pregnancy.

In Table II a comparison is made of the number of hospital post-operative days, the operating time, and the average morbidity in the two types of operation.

TABLE II

	CLASSICAL (113 CASES)	CERVICAL (51 CASES)
Days in hospital	20 days	20 days
Average postoperative Temperature above 100.4° F. after first 24 hours— average days per case	3.6 days	3.44 days
Operating time	39.5 minutes	49.6 minutes

TABLE III. MORBIDITY

	CLASSICAL (113 CASES)	LOW CERVICAL (51 CASES)
Wound infection	9	2
Pneumonia	3	1
Retained lochia	2	2
Pyelitis	2	0
Ruptured wound	1	0
Thrombophlebitis of veins in leg	3	1
Pulmonary embolism	4	0
Mastitis	1	0
Intestinal obstruction with peritonitis	2	0
Toxic ileus and sepsis	1	0
Acute ileus	1	0
Undetermined	2	3

It is interesting to note that there were 4 cases of pulmonary embolism in the classical group and none in the low section group, and 3 cases of thrombophlebitis of the veins of the leg following the classical section to one in the low section. In this small series thrombosis and emboli were more common in the classical group, and it may be that the location of the incision in the contractile portion of the uterus near the venous sinuses is the explanation. There were 2 cases of intestinal obstruction with peritonitis in the classical group and none in the low group. Here again it would appear that the high location of the wound in a uterus which almost immediately starts contracting and relaxing after it is emptied would not favor primary union. This would in turn favor the passage of lochia into the general peritoneal cavity thus permitting the development of peritonitis, adhesions, and intestinal obstruction.

TABLE IV. MATERNAL MORTALITY

	CLASSICAL SECTION (113 CASES)	LOW CERVICAL SECTION (51 CASES)
Cardiac decompensation	1	0
Toxemia of pregnancy, premature separation of placenta, and suppression of urine	1	0
Toxic ileus	1	0
Sepsis and paralytic ileus	1	0
Pulmonary embolism	2	0
Intestinal obstruction	2	0

There were 8 deaths following the classical operation and none following the low section. The death which resulted from cardiac failure and the one following toxemia of pregnancy complicated by premature separation of the placenta would undoubtedly have occurred regardless of the type of operation. However, it is quite likely in some of the other 6 patients that the outcome would have been different had a low cervical section been done.

FATALITIES

CASE 1.—A. M. (Unit 35995.) A classical section and Pomeroy sterilization under local anesthesia were done on a primipara, aged 20 years, within two weeks of term. The indication was congenital heart disease with symptoms of decompensation. She died of cardiac failure eight hours after the operation.

CASE 2.—J. McG. (Unit 60932.) A classical section was done on a primipara, aged 25, on Aug. 12, 1934; she was 7 weeks premature. The indication was toxemia of pregnancy complicated by concealed hemorrhage due to a premature separation of the placenta. At operation much fluid blood and clots escaped from the uterus under tension. The uterus showed many petechiae and a few larger areas of ecchymosis. The left broad ligament was hemorrhagic. About eighteen hours later she vomited 12 ounces of bloody fluid but was apparently doing well. She developed a suppression of the urine and all treatment directed to this was of no avail.

CASE 3.—A. J. (Unit 43420.) A classical section was done in a primipara, aged 25, at term Feb. 13, 1931. The indication was a contracted pelvis following a twelve-hour test of labor with membranes intact. The patient did poorly after operation, soon developing abdominal distention, vomiting, and a moderately high fever. These symptoms persisted and she died six days postoperatively with a diagnosis of toxic ileus.

CASE 4.—B. H. A classical section and Pomeroy sterilization were done May 18, 1934, on a para v at the onset of labor. The indication was two previous sections. She did poorly soon after the operation, developing a rapid pulse, a high temperature, vomiting, and abdominal distention. A diagnosis of paralytic ileus was made. She died five days postoperatively. At autopsy pus was found in the abdominal wound and in the uterine wound. Several coils of small gut were densely adherent to the abdominal wall. There were some blood clots and free blood in the peritoneal cavity probably due to a ligature slipping over the resected portion of the left Fallopian tube. This hemorrhage only partially accounted for her death, sepsis and paralytic ileus being the actual causes.

CASE 5.—A. N. (Unit 48706.) A classical section for nephritic toxemia two weeks before term was done on a para i, aged 32, two hours following spontaneous rupture of the membranes. Postoperatively, the patient had a moderately febrile reaction every day, but it was thought that she would recover. On the fifteenth day she developed a pulmonary embolism and died fourteen hours later.

CASE 6.—B. S. (Unit 12153.) A classical section was done on a primipara, aged 39, at term Sept. 17, 1927. The indication was poor progress in an elderly patient. Membranes had been ruptured twenty-four hours with fairly active labor for twenty-four hours. Her postoperative course was uneventful and afebrile until the fifth day when she developed symptoms of acute collapse with pain in the right shoulder, cyanosis, and a rapid pulse and a temperature. She died eighteen hours later. Diagnosis: Pulmonary embolism.

CASE 7.—A. D. (Unit 42448.) A classical section was done on a primipara, aged 36, at term on Nov. 30, 1930. The indication was a big baby with a breech presenting in an older patient who made unsatisfactory progress. Rupture of the membranes and active labor had existed seventeen hours. She had a very stormy postoperative course, developing pulmonary collapse and lobar pneumonia. A laparotomy was done twenty-three days following the section for an acute intestinal obstruction due to adhesions. There was considerable exudate in the pelvis. She died two weeks following this and thirty-seven days following the section.

CASE 8.—V. L. (Unit 40843.) An elective classical section was done on a para ii, aged 31, on Aug. 15, 1930, two weeks before term. The indication was a previous section. On the seventh day following operation a diagnosis of complete obstruction was made and at laparotomy the obstruction was found to be due to an adhesion between the small intestine and the parietal peritoneum. The adhesion was released but the patient died twelve hours later. Diagnosis: Intestinal obstruction.

SUMMARY

Cesarean section in this series resulted in a high maternal mortality. This may be due to the relatively large number of classical operations performed. During the past four or five years we have done fewer classicals and more cervical sections, and this has resulted in a definitely lower maternal mortality.

In this group the more serious complications such as ileus, pulmonary embolism, thrombophlebitis of the veins of the leg, peritonitis and intestinal obstruction occurred relatively more frequently following the classical operation.

There were eight deaths all of which followed the classical operation.

Sections were done for 3 ruptured uteri all of which were subsequent to previous classical operations.

Two patients were operated upon for acute intestinal obstruction during the post-partum period because of bands of adhesions. Two other patients developed acute intestinal obstruction due to adhesions some time after discharge from the hospital. All of these occurred after classical sections. It appears that the troublesome adhesions are more likely to develop following the classical operation.

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THE EXPERIMENTAL PRODUCTION OF INTERSEXUALITY IN THE FEMALE RAT*

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PARTIAL or complete sex reversals have been found in almost all classes of animals. In the human being, there are innumerable cases of pseudohermaphrodites reported. About 30 cases of true hermaphrodites, that is, individuals having gonads of both sexes, are considered as authentic.¹ Many theories have been presented in explanation of these abnormalities and much work has been done in attempts to reproduce them in experimental animals. Such procedures have been almost uniformly unsuccessful in mammals. In contradistinction to the mammalian experiments, very striking results have been obtained with amphibia and birds. The developing embryos of these animals are self-sufficient units, and, as such, are capable of being influenced by operative procedures and by environmental changes. The mammalian embryo is so situated that procedures which might conceivably alter its sexual differentiation interfere either directly with its own viability or with the life of its host, the mother.

The classic experiment in the field of mammalian intersexuality is that performed by nature, the production of the "free martin." The free martin is one member of twins in cattle, the other member is a normal male. Genetically a female, the free martin is masculinized to varying degrees. There is an atrophy or lack of development of Müllerian duct derivatives (oviducts, uterus, and upper vagina). The Wolffian duct derivatives (epididymis, vas deferens, seminal vesicles, and ejaculatory ducts) are usually present. The external genitalia (urogenital sinus and genital tubercle derivatives) are usually feminine in appearance and changes in the gonads are usually found. It has been established by Lillie and his co-workers that the free martin is produced only when there is an anastomosis between the placental vascular systems of the embryonic male and female.²⁻⁴ He has theorized that an hormone from the male reaches the female via the interconnecting blood supply. This "male sex hormone" inhibits the Müllerian or female duct derivatives and stimulates the Wolffian or masculine duct derivatives.² Thus a masculinized female or intersexed animal results.

In the early, sexually undifferentiated embryonic state, the Müllerian and Wolffian ducts co-exist, and up to a certain period the embryo is equipotential as to future sexual development. That is, the anlage of both male and female sexual systems is present. Inasmuch as the gonad of the male differentiates into a testicle earlier than the gonad

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of the female differentiates into an ovary, it is possible that the "male hormone" being formed first should have a directive influence on the development of sexual structures in the female twin, inhibiting female structures and stimulating male structures.

Attempts to influence sex development in amphibia and birds by administering sex hormones to the developing embryo have been successful. Partial (intersexes) and complete sex reversals have been obtained by this method in both amphibia and birds.⁵⁻¹⁸ Attempts to influence sexual differentiation of the mammalian embryo by administering sex hormones to the pregnant mother have met with slight success. Evidence has been presented, however, that development of the external genitalia of female rats can be permanently modified by giving large doses of estrogenic substance to the pregnant mother of these animals during the last few days of her pregnancy.¹⁹⁻²³ The lesion produced is a marked hypospadias (the female rat normally has a complete clitorine urethra). While this modification is a permanent arrestment of the caudal portion of the urogenital sinus, it can hardly be considered in the light of an intersexual change. The male has only been slightly affected. The amount of female sex hormone that can be given to the pregnant rat is limited. Large doses, given early enough in pregnancy to conceivably feminize the male embryo, have caused resorption or abortion of the pregnancy in our experimental work to date.

In view, however, of the very definite effect of estrogenic substance on the development of the external genitalia of the rat, it was hoped that male sex hormone might have an analogous action, and might even influence the development of the female embryo sufficiently to produce some evidence of true intersexuality. The rat is a good subject for such an experiment. Its gestation period is short (twenty-two days), and its embryonic development is relatively slow. Implantation takes place on the fifth day,²⁴⁻²⁶ and a placenta like that of the human being, with chorionic cells in direct contact with the maternal blood stream, is developed. The indifferent gonad starts to differentiate into a testis late on the fourteenth day.²⁷ If the gonad is to be an ovary it does not start to differentiate until the seventeenth day.²⁷

EXPERIMENTS AND RESULTS

Pregnant rats have been injected with testosterone and testosterone propionate. Varying doses have been given at different periods of the last third of the pregnancy by single or multiple injections. The pregnancy of the majority of these treated animals has been terminated by resorption or abortion. Of 152 animals treated, 55 have delivered at term, spontaneously or by cesarean section. The female offspring of 45 of these litters have shown varying degrees of masculinization. Apparently subthreshold dosages were responsible for lack of masculinizing changes in the females of the 10 remaining litters. Sixty-four newborn and 40 adult intersexed animals have been studied by gross and microscopic dissections. Histologic specimens and whole mounts have been prepared, and wax plate and graphic reconstructions have been made. The degree of masculinization seems to vary with the amount of male sex hormone given and also with the period of pregnancy when treatment is administered. A difference in response between litters is noticeable, but there are only slight variations between females of the same litter.

Changes in the external genitalia vary. Small dosages inhibit development of the vaginal introitus so that the external vagina is represented by a crescentic skin

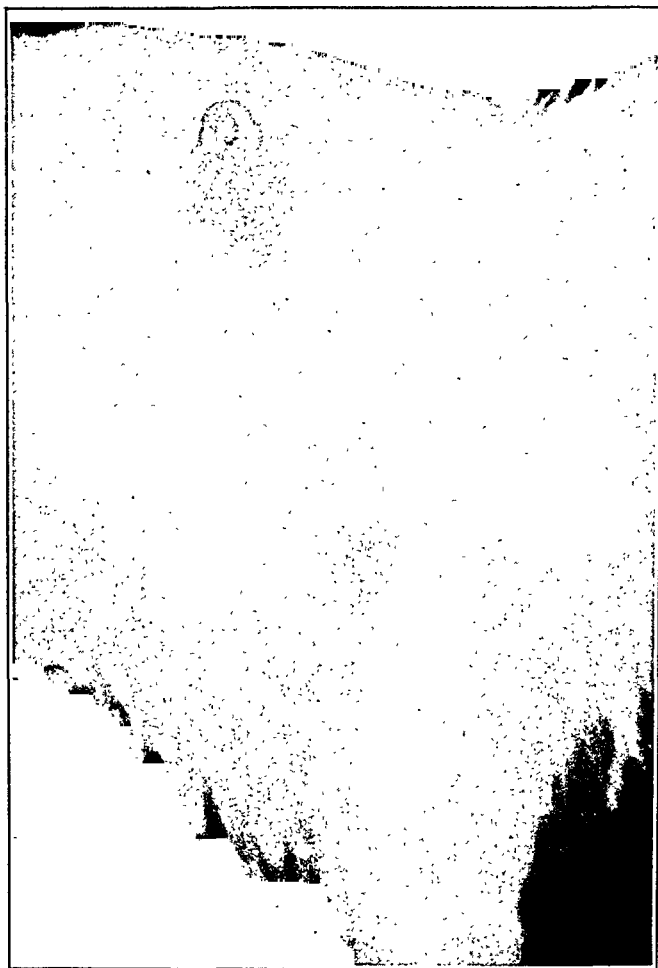


Fig. 1.—External genitalia of intersexed Rat 29-A. Animal has no vaginal orifice. Penis is shown everted.

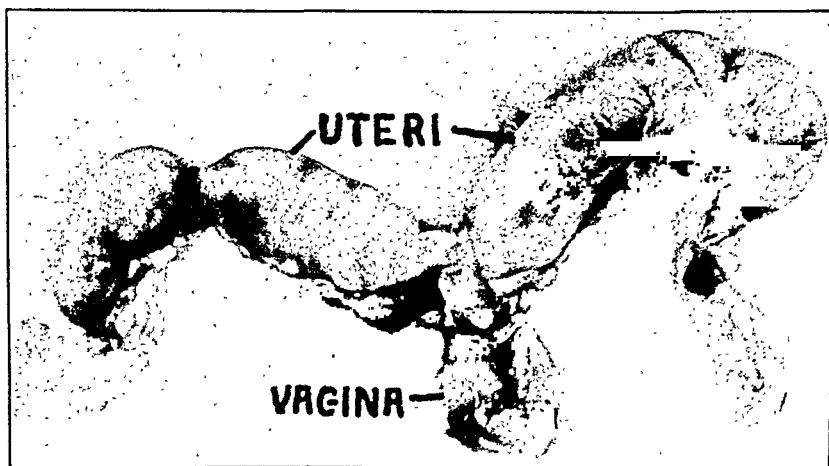


Fig. 2.—Dissected genital tract of intersexed Rat 69-B. Uteri and vagina are greatly distended with retained secretions because no patent vaginourethral communication is present.

fold embracing the caudal base of the phallus which is hypospadiac. Larger doses cause the production of a penis with a nonpatent "skin fold." With still larger dosages, the external vagina is completely absent and the phallus is a small but apparently normal penis (Fig. 1). An os priapi which is present in the normal male rat is also found in the penis of these intersexed animals.

Changes in the internal genitalia are equally striking. The lower part of the vagina is completely absent with the higher dosages. In some animals the upper

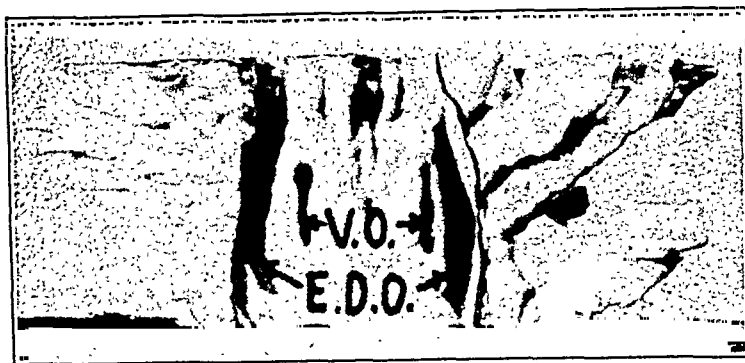


Fig. 3.—Wax plate reconstruction of part of the urogenital region of adult intersexed Rat 29-A. The front of the urethra has been cut away to show the vagina emptying into the urethra by bilateral ostia. V.O., vaginal orifices; E.D.O., ejaculatory duct orifices.

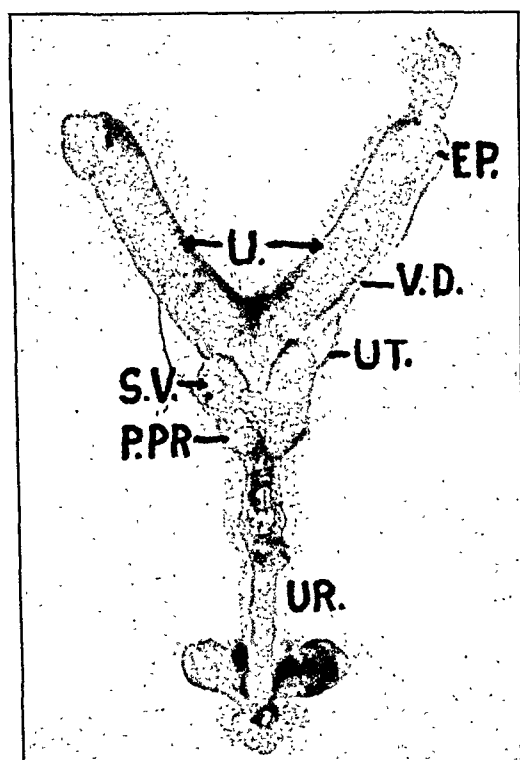


Fig. 4.—Dissection of genital tract of intersexed Rat 80-B. (dorsal view). Left gonad was removed for histologic study. U., uteri; V.D., vas deferens; EP., epididymis; S.V., seminal vesicle; P.PR., posterior prostatic lobe; UR., urethra, UT., ureter.

two-thirds appears to end blindly. In these animals the uteri and upper vagina are markedly distended with retained secretions (Fig. 2).

In other animals whose mothers have received still higher dosages, the vagina communicates with the urethra by bilateral ostia medial to the ostia of the ejaculatory ducts. A wax plate reconstruction of this region has been made from serial sections of one of these adult animals (Fig. 3). This condition is interpreted as a preservation of the original bilateral communications of the Müllerian ducts with the urogen-

ital sinus. Serial sections and wax plate reconstructions reveal similar conditions in the newborn affected animal. In some, the bilateral junctions of the vaginal epithelium with the epithelium of the urethra are not patent, but in others they are patent.

Combined with the agenesis of the distal part of the vagina, there is a development of masculine urogenital sinus derivatives. In well-modified animals all the various prostatic lobes are found. In less well-modified animals fewer lobes are present; in some cases prostatic development is represented by the presence of ventral lobes alone. These lobes (para-urethral glands) have been observed macro-

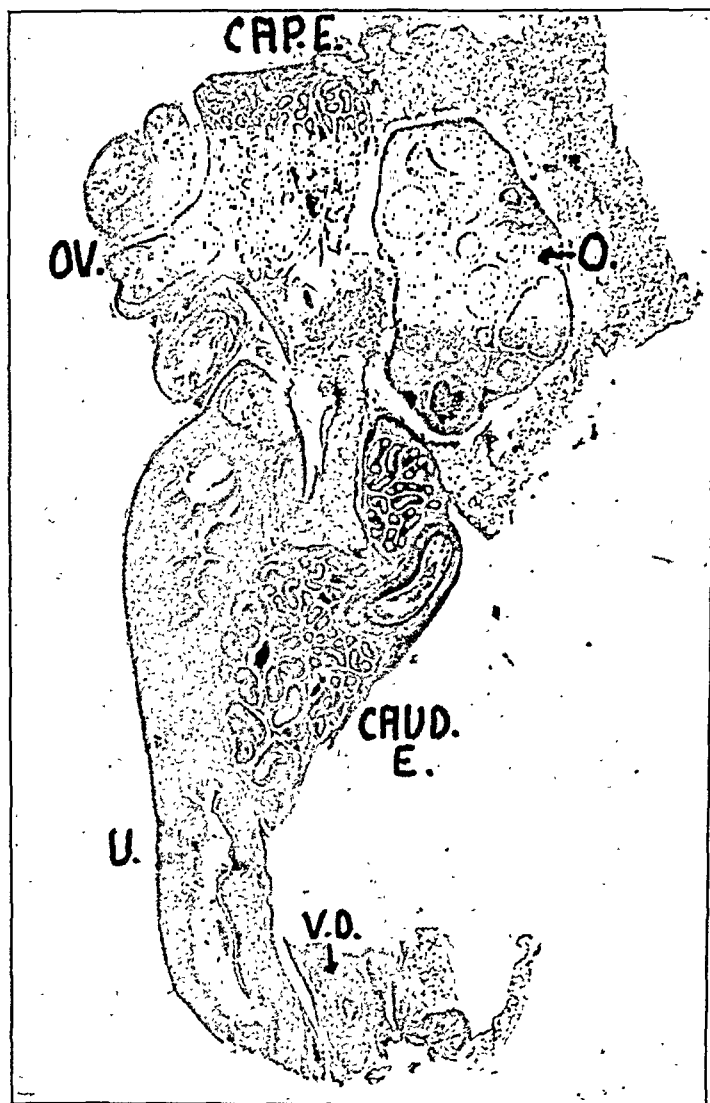


Fig. 5.—Section through left gonad region of young intersexed Rat 80-A. O., ovary; OV., oviduct; U., uterus; V.D., vas deferens; CAP.E., caput epididymis; CAUD.E., caudad epididymis.

scopically in experimental animals having no other internal or external genital abnormality. In the normal adult female they are usually not grossly visible but have been reported as present in the majority of normal females treated with large doses of male sex hormone.^{28, 29}

Complete Wolffian duct derivatives have been found as bilateral structures in 6 adults and as unilateral structures in 2 adults. These derivatives include head and tail of the epididymis, vas deferens, seminal vesicle, and ejaculatory duct (Figs. 4 and 5). Efferent tubules connect the head of the epididymis with the rete of the gonad.

ficient stimulation of them may and can occur and the clinical syndrome persists. If this area of the ovaries described by Dr. Ramsay as the usual site of the rete ovarii is excised, we are definitely removing a probable cause and thereby lessening the chance of unsuccessful surgical therapy.

Adrenal cortical disorders occupy an important place in the differential diagnosis of obstetric and gynecologic conditions. Therefore I feel this evening's presentations are a definite advancement towards our clinical understanding of this very important group of pituitary-adrenal-gonadal disorders.

DR. RAMSAY (closing).—Among the many descriptions of the origin of male interstitial cells, origin by direct transformation of the interstitial connective tissue cells is a most interesting and probable one. During inflammatory processes in the testis, series of close transitions between connective tissue and male interstitial cells have been seen. Such possibilities, no doubt, explain the facility with which the interstitial cells may fluctuate in number. The suggestion that these cells develop from the original gonadal genitaloid cells not included early in testis tubules, I think, should not be cast aside.

In all fairness to those holding opposite views, I would like to mention that the actual function of the interstitial cells has been questioned, particularly those of the female. It is well known that interstitial cells in the human ovary (admittedly homologues of male interstitial cells) are extremely rare and may be absent entirely. Such individuals exhibit no lack of proper female characteristics.

Embryologically, there are three materials which may be considered as containing masculinizing factors. First, in the gonads, there are two parts: the tubules and the interstitial cells; and second, as has been mentioned, the adrenal cortical material. The virilistic effects of the adrenal cortex have been explained as due to its proximity in origin to the gonadal anlagen. Such an explanation is, however, quite obscure and inadequate. A functional linkage between gonad and adrenal cortex, although elusive so far, is strongly suggested. In the normal ovaries used in this study, adrenal cortex is absent.

DR. McCahey (closing).—With regard to what has been said about removal of tumors of the adrenal without beneficial results, it is quite possible that, in such instances, the virilism persists because of endocrine activity of testis tissue in the ovary. It is also conceivable that removal of an ovarian tumor would not completely relieve virilism and the reason might be that testis tissue in the mesovarium was left behind.

I must disagree with Dr. Mazer's statements. There is abundant experimental evidence that testis hormone causes masculinization. For example, the ordinary barnyard hen has a functioning ovary and a rudimentary ovary. If the good ovary is removed the rudimentary ovary may develop into a testis-like organ. This is due to growth of tissue representative of the primary gonad in the ovary. The bird will then develop all the characteristics of a rooster but is, nevertheless, genetically a female. In a recent issue of *Endocrinology* an experiment was reported in which it was found that implantation of ovaries into the ears of castrated male mice prevented the atrophy of the prostate and seminal vesicles which invariably follows castration. It seems likely that the explanation of this finding is that the implantation of the ovaries into the particular site chosen, which would have a temperature comparable to that of the scrotum, permitted the testis remnants in the ovary to remain active.

Dr. Mazer also states that he finds that when he injects large amounts of testis hormone into women they do not develop virilism. I would like to point out that similar injections into men with the symptoms of hypogonadism have practically no effect. It appears that the commercial preparations of testis hormone at present available are not potent therapeutically.

In his discussion Dr. Mazer said repeatedly that it was not possible to use more than one or two animals in the urinary assays for testis hormone. It is our practice to use three or more birds for each assay. We have never reported a finding based on the result obtained in one capon. A few of our assays are based on the response obtained in two capons but such were due to the fact that one of the trio originally injected was found to be unsatisfactory for test purposes.

has been found in 23 newborns (Figs. 6 and 7). A detailed study of the gonad and its accompanying tubules has not yet been made.

In a preliminary report on this subject,³⁰ it was stated that evidence of Müllerian duct inhibition had been found. Such evidence has been limited to that found in serial sections of 2 newborns. In all other newborns and in all adults to date, oviducts and uteri (the rat has a double uterus) have been present.

DISCUSSION

Other investigators have given androgenic substances to pregnant rats. Hain obtained resorptions with testosterone but noted a few successful deliveries with some of the synthetic androgens.³¹ She apparently did not study these offspring. Scipiades, in studying the effect of testosterone and testosterone propionate on the length of pregnancy, reported several deliveries of living young but made no remarks as to their morphologic condition.³²

While our work was in progress, Dantchakoff reported changes similar to ours in the forty-five-day embryonic female guinea pig. She obtained these changes by injecting solutions of testosterone propionate directly into the amniotic cavity of the fifteen-day intrauterine embryo. She has not reported any changes in adult animals to our knowledge. The presumption is that none of her animals survived to term.³³⁻³⁶ Since our preliminary note on this subject, our findings have been confirmed in the mouse by Raynaud³⁷ and confirmed in part in the rat by Hamilton and Gardner.³⁸

These findings seem to confirm Lillie's theory that it is a "male sex hormone" from the embryonic male that is responsible for the masculinization of the genetic female twin (free martin). However, certain differences exist between the free martin and our masculinized females. In the free martin, the Wolffian duct derivatives (the vas deferens, seminal vesicles, etc.) are stimulated, whereas, the Müllerian duct derivatives (oviduct, uterus, etc.) are inhibited. Its urogenital sinus and genital tubercle derivatives are usually not affected. Our animals show stimulation of Wolffian duct derivatives, but display little inhibition of Müllerian duct elements. The entodermal urogenital sinus derivatives show most marked changes. Two explanations for these differences may be advanced: (1) The male hormones in the two cases are not identical, since one is derived from embryonic testes and the other is an adult testicular principle; (2) the hormones are identical, but in the experimental animals the hormone is not effective as early nor for as long a period as in the free martin. Also, the total quantity of hormone acting on our animals may be less than in the free martin.

In well-masculinized animals only the upper two-thirds of the vagina is present. In some it ends blindly, in others the distal end communicates with the urethra by bilateral ostia. The remainder of the urethra presents a purely masculine appearance. In order to explain this condition, it is necessary to assume that the urogenital sinus is originally bipotential with respect to its sexual differentiation. It may give rise to the urethra, vestibular (Bartholin's) glands, lower vagina and other structures in the female, or it may give rise to the urethra, prostatic diverticula, Cowper's glands, etc., in the male. Interference with the

In less well-modified females, only seminal vesicles and ejaculatory ducts are present. The various prostatic lobes have been found with no preservation of the Wolffian duct derivatives.

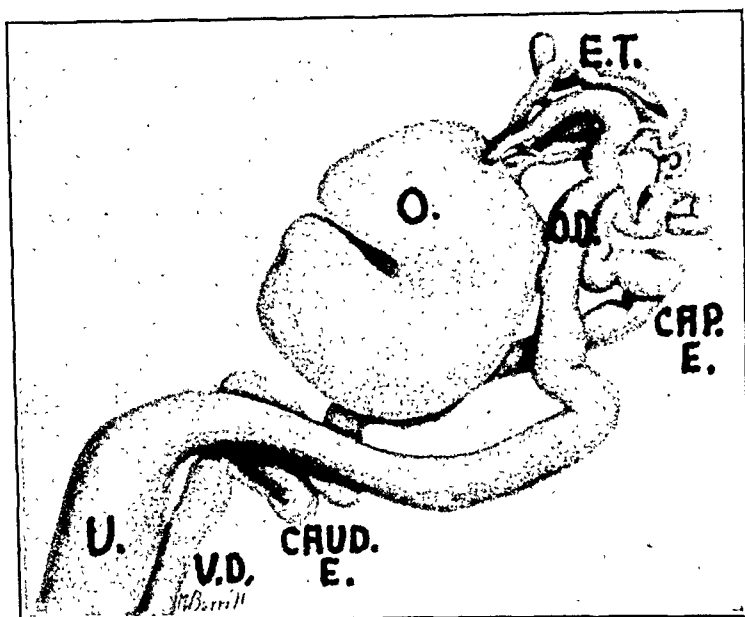


Fig. 6.—Left gonad region of newborn intersexed Rat 93-A. Drawing based on graphic reconstruction. O, ovary; E.T., efferent tubules; CAP.E., caput epididymis; CAUD.E., caudad epididymis; O.D., oviduct; U., uterus; V.D., vas deferens.

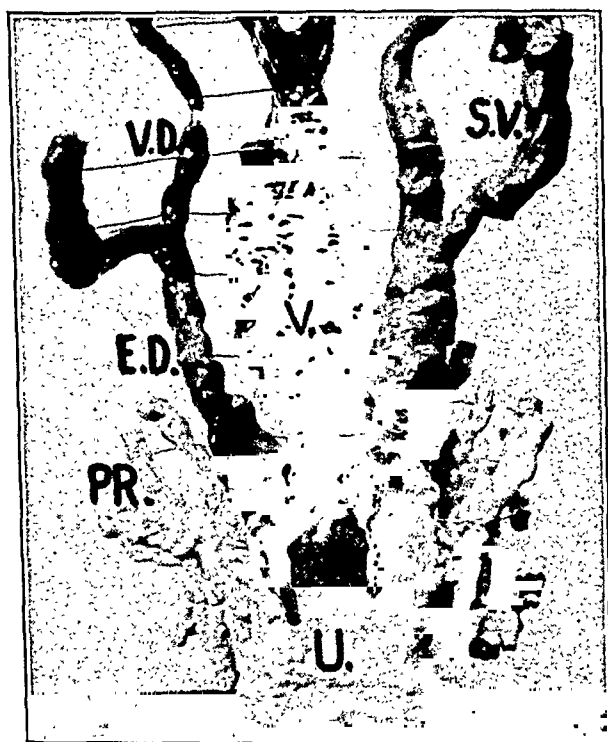


Fig. 7.—Wax plate reconstruction of part of urogenital region of newborn intersexed Rat 60-A. (dorsal view). The vagina of this rat communicates with the urethra bilaterally, but these communications are not patent. V., vagina; V.D., vas deferens; S.V., seminal vesicle; E.D., ejaculatory duct; P.R., prostatic diverticula; U., urethra.

Complete unilateral persistence of the Wolffian duct from gonad to urethra with anlage of efferent tubules, epididymis, seminal vesicles, and ejaculatory ducts, has been identified in 10 newborns. Complete bilateral persistence of these structures

embryonic development of genetic females is so modified that uteri, oviducts, and upper vagina; combined with epididymis, vas deferens, seminal vesicles, ejaculatory ducts, the various prostatic lobes, Cowper's glands, and a penis are found in the same adult animals. Indicative evidence that the lower part of the vagina is derived from the urogenital sinus in the rat is presented. It is suggested that an excess of androgenic substance in the human pregnant organism may be the causal factor in the production of some human intersexes.

The crystalline testosterone and testosterone propionate used in this work were generously supplied by the Schering Corporation and Ciba Pharmaceutical Products Inc.

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From their studies the authors show that acute inflammatory diseases of the female genitalia result in a marked sensitivity to insulin. This is the result of the decreased ability of the liver to store glycogen. Such a reaction could not be demonstrated when the inflammatory process was subacute or chronic. When the inflammatory process is virulent and widespread, the intermediate metabolism is disturbed as a result of damage to the liver parenchyma. No liver change could be demonstrated in extrauterine pregnancy. The resulting icterus must therefore be a hemolytic one rather than one of liver origin.

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normal course of development in the genetic female by an excess of male sex hormone, then, would cause inhibition of the feminine tendencies (absence of lower vagina) and stimulation of the masculine tendencies (presence of prostates, etc.). The bilateral communications of the upper vagina with the urethra in some of our affected animals can only be interpreted as a persistence of the original junctions of the Müllerian ducts with the urogenital sinus. Thus the incomplete vagina which is found in these animals represents that portion of the normal vagina which is derived from the Müllerian ducts. The lower portion which has been inhibited must, therefore, normally arise from the urogenital sinus. This interpretation is at variance with some theories concerning the normal derivation of the vagina, although Koff³⁹ has found that the lower segment of the human vagina is derived from the urogenital sinus. Embryologic studies on the rat are being made to ascertain the accuracy of our hypothesis.

During the progress of this work, 2 cases of arrested development of the lower vagina in human beings, similar to the findings in our rats, have been brought to our attention (through the courtesy of Drs. H. O. Jones, Harry Culver, and W. T. Carlisle). These children had hypospadiac, penislike organs and apparently normal ovaries, Fallopian tubes, and uteri. Only the upper portion of the vagina was present, and it communicated with the urethra about 1 inch from the urethral meatus. So far as could be determined by palpation and abdominal exploration, no prostates or seminal vesicles were present. Hugh Young has reported 6 human beings with similar vaginourethral communications.⁴⁰ Von Neugebauer has reported many such cases.⁴¹ Several of these cases that came to the autopsy table were thoroughly dissected, and prostates and seminal vesicles were found.^{40, 41}

Womack and Koch first reported in 1930 that a substance having properties of the male sex hormone was found in normal human female urine and in normal human pregnancy urine.⁴² It is most interesting that this androgenic substance is not only present in normal human female urine, but that it is present in very nearly the same concentration that it is found in normal human male urine.⁴³ Estrogenic substance (female sex hormone-like substance) is found in normal male urine.⁴³ The concentration of estrogenic substance is relatively higher, however, in female urine than in male urine.⁴³ Androgenic substance has been found in normal human placentas^{44, 45} (and unpublished observations of the author). These facts make the results of our experimental work on rats of more than academic interest. Large amounts of androgenic substance injected into the mother rat have so influenced sexual development of the embryo that a masculinized female or an intersexed animal has resulted. It is conceivable then, that an *excess* of androgenic substance circulating in the pregnant human female may so influence sexual differentiation of the embryo that a masculinized human female or an intersex results.

SUMMARY

The production of intersexed rats by the administration of male sex hormone to the pregnant mothers of these animals is reported. The

was reduced into the abdomen and removed with its pedicle (Fig. 2). The gall bladder, liver, kidneys, and suprarenals were cursorily palpated and presumed to be normal. A prophylactic appendectomy was done, the hernia repaired, and the abdomen closed. The convalescence was satisfactory.

Pathologist's Report.—The external coat of the testis was composed of a dense, very cellular, fibrous tissue stroma, containing single smooth muscle fiber cells and moderately dilated capillaries. The larger blood vessels lying deeper in this capsule had moderately thickened walls, and surrounding them were small islands of nerve bundles and also islands of epithelial-like cells with large round to

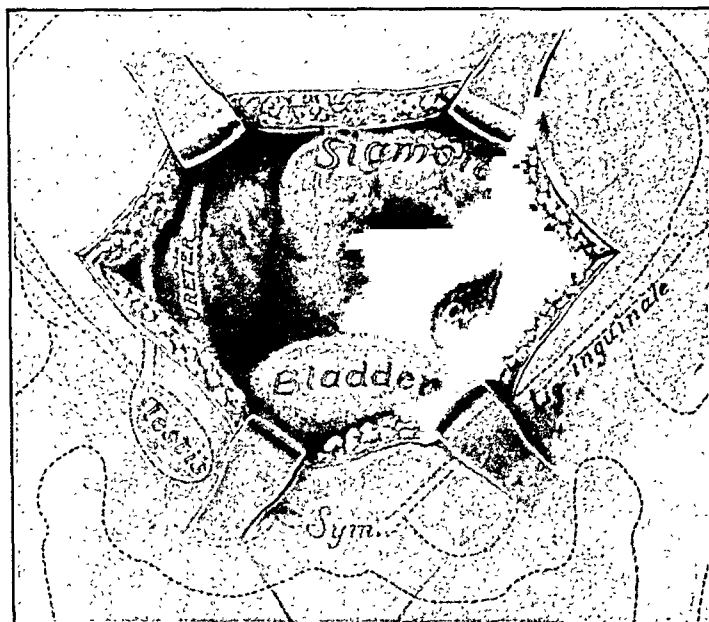


Fig. 1.—Showing findings at operation. The designation *Ov* on the left should be gonad, as no histologic proof was obtained that the tissue was ovarian.

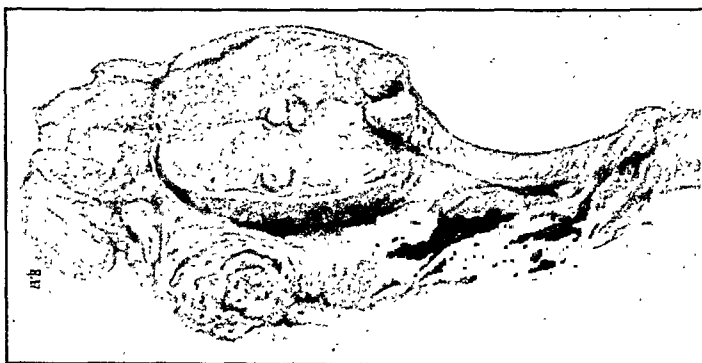


Fig. 2.

oval nuclei. The cytoplasm was slightly granular and in places vacuolated and also contained small brownish looking granules. The nucleus was composed of a finely reticulated chromatin material. In the deeper portions of the section there were islands of tissue composed of single tuboglandular structures lined by a high columnar epithelium with slightly elongated nuclei. The cell membranes of these cells were indistinct and their lumina appeared to be occluded (Fig. 3).

The chromatin of the nucleus was considerably more dense than those cells described above. About these tubular structures was a fairly dense capsule of connective tissue, containing swollen fibrocytes with pale staining oval to elongated vesicular nuclei. Surrounding these isolated tubular structures were large numbers

TWO CASES OF INTERSEXUALITY*

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THE term "intersex," according to Goldschmidt, refers to those individuals who started out either male or female from a genetic standpoint but who, after a certain period, completed their sexual development in the opposite direction. In the intersex there is first a female phase and later a male phase, or vice versa, and in the second phase a typical mixture of both sexes exists. All true and pseudo-hermaphrodites are intersexes genetically.

It is exceedingly difficult to define sex from a biologic viewpoint and, according to Lillie, there is no such entity but rather a dimorphism into contrasting characters, whether they are biologic or psychologic. In a general way, sex is a fundamental attribute of nature and the exact mechanism is not fully known, although a special capacity of protoplasm, a regulatory force from the chromosomes, genes, and endocrine glands as well as environmental factors in the production of sex have been alluded to. Sexual deviations with the production of intersexes may then result from some unusual condition of the above four factors.

The following cases are presented because of certain recent investigations which seem to shed more light on their evolution, and also because we encountered problems in surgical procedure which did not seem to be sufficiently defined.

CASE 1.—J. L., a white female aged twenty years, married six months, entered the hospital Dec. 21, 1936, complaining of swelling in the right inguinal region for the past fifteen years which, for the past two months, had been painful. She stated that she had never menstruated. Coitus was painful but was undertaken about twice weekly. The patient had always been healthy, even escaping most of the childhood diseases. There was no family history suggestive of hermaphroditism, carcinoma, or syphilis, and venereal disease was denied.

Physical examination revealed an individual whose appearance was quite feminine. There was no evidence of hair on the face, chest, or in the axillae; only a few scattered black pubic hairs were noted. The hands and fingers were somewhat masculine in type, but the feet were distinctly feminine in size and shape. No laryngeal prominence was evident. The voice was that of a woman. The breasts were symmetrical and well developed. In the right inguinal region there was an egg-sized mass which was tender, mobile, not reducible to the abdominal cavity, and gave a distinct impulse on coughing. The left inguinal canal was normal. The appearance of the external genitalia, except for the absence of hair, was essentially normal. The clitoris appeared normal in size and in its relation to the urethral orifice. Skene's ducts and Bartholin's glands were not palpated. The vagina was short but elastic. Rugae were well established. The uterus was apparently absent. The adnexa were not palpated.

Laboratory findings were as follows: Blood pressure 120/80; hemoglobin (Sahli) 80 per cent; erythrocytes 4,500,000; leucocytes 7,400. X-ray picture of the sella turcica was negative; x-ray picture of the pelvis suggested masculinization. Basal metabolic rate was plus 4.

A diagnosis was made of the right inguinal hernia, Müllerian duct agenesis.

The patient was submitted to operation on Dec. 23, 1936. A modified Pfannenstiel's incision was extended to expose the right inguinal region. The abdomen was opened (Fig. 1). There was no evidence of uterus, Fallopian tubes, or vestigial structure. The left gonad was smooth, rounded, about 2 cm. by 3 cm., opalescent; no follicles were evident. It was attached to the wall of the pelvis by rather a firm band of peritoneum, resembling an atrophic infundibulopelvic ligament. On the right side a somewhat similar structure was prolapsed into the inguinal canal. This

*Presented at a meeting of the Chicago Gynecological Society, April 15, 1938.

mother noted that the clitoris was enlarging and becoming penislike. This continued to grow and erections were disturbingly frequent. To avoid the neighbors becoming aware of her problem, she had not permitted the child to play with other children and had kept the same maid. She described in tragic detail the fears of a parent with a child of undetermined sex. During the past year itching and dysuria had been noted occasionally and "pus in the urine" was found twice by the family doctor. Measles, frequent respiratory infections, chronic constipation, and three convulsions constitute her medical past. Her brother was nine years of age and was precociously developed; axillary and pubic hair was well established. The maternal grandmother had diabetes. The mother had repeatedly taken thyroid extract and was taking thyroid while pregnant with this child.

The general examination revealed a well-developed, well-nourished child who appeared distinctly feminine. The abnormalities noted in the teeth were some separation of the incisors; in the hands there was a slight incurving of the last phalanges of the little fingers. Both hands were broader than normal. The body weight, height, and trunk extremities were normal. The laryngeal prominence was not palpated. On inspection of the genitalia, there was an abundant growth of thin, brown curly hair about the vulva. The clitoris was a dangling penislike structure with a somewhat redundant prepuce. At its base there was an opening, the urethra. There was a suggestion of labia majora but no labia minora, hymen, or vaginal orifice. Bimanual palpation through the rectum detected a small uterus. The ovaries were not palpated nor was there any structure suggestive of a prostate.

Cystoscopic Report by Dr. Harry Culver: By hugging the roof of the urethra, a No. 21 F. cystoscope was readily passed into the bladder which appeared to be normal. On the floor of the urethra, 2 cm. from the vesical orifice, was an opening. Through this the cystoscope passed for a distance of 3 cm. into a pouch lined by typical vaginal epithelium. The opening of the vagina into the urethra was 2 cm. distant from the urinary meatus.

Laboratory Findings.—Repeated urinalyses, blood and stool examinations were normal. Blood chemistry: nonprotein nitrogen 33 mg., sugar 93 mg., cholesterol 140 mg. per 100 c.c. of blood; sugar tolerance 93, 108, 93, 91. Wassermann negative. Basal metabolic rates were minus 30 and minus 23. Cholesterol determinations on the same days were 140 and 154. Hormone studies by Dr. Barnes showed androsterone 0.2 mg. and a trace of female sex hormone.

A diagnosis was made of female pseudohermaphroditism with masculinized external genitalia.

On Nov. 29, 1937, a laparotomy was done for further study of the internal organs. There were an apparently normal uterus, tubes, and ovaries with normal relations and ligamentous supports. Two punch biopsies were taken from the right ovary. As the left ovary was identical, it was not disturbed. Careful search was made for other gonadal structures. Dr. Culver palpated the kidneys and suprarenals and believed them to be normal. A prophylactic appendectomy was done. The abdomen was closed and the phallus removed according to the technic of Hugh Young. The convalescence was satisfactory.

The histologic report of the ovarian biopsies was normal ovarian tissue with many miniature Graafian follicles. The embryologic explanation of this case is that there was apparently an inadequate stimulus for development of the sinovaginal bulb into the normal structures of the external genitalia. The Müllerian tubercle and urogenital sinus, instead of descending to form the vulval cleft, remained in the position of much earlier development, so the external evidence of a vagina was not present.

The next problem was the determination of the optimum time in this child's life for the reconstruction of the vagina. In reviewing other case reports of this condition, which is by no means a rare one, we were unable to find any discussion or reference to the time when a vaginal plastic of this type would be most likely to afford a good functional result. From a psychologic viewpoint, the earlier the time the better. The external genitalia of this child are now, however, not unlike a normal female child.

of cells with rather distinct cytoplasmic membranes and a distinct vacuolated cytoplasm. The nuclei of these cells were round to oval and vesicular with a reticulated chromatin network. Dispersed throughout these cells were small capillaries lined by a moderately swollen endothelium and supported by fine strands of connective tissue with swollen nuclei.

In addition, there were other islands composed wholly of a tubular adenomatous structure containing a more clearly defined lumen. The cells were columnar, the nuclei were oval in shape and similar to those described in the other islands of tissue.

Some of these cells formed solid cords and were separated from each other by dense infiltrations of connective tissue stroma containing large, elongated and slightly oval and occasionally irregular nuclei. These islands, however, were devoid of the epithelial-like cells that formed the interstitial stroma described in the other islands. Here and there one could see transitional stages, varying from just tubular structures to where occasional tubular structures were seen surrounded by large numbers of cells, Leydig-like in appearance and similar to those described above.

After van Gieson stain, the islands were composed wholly of tubular structure containing much connective tissue, whereas those containing Leydig's cells contained only fine strands of collagen fibers.



Fig. 3.

Sudan III stain revealed the Leydig fat cells filled with many fine sudanophilic droplets. Here and there were small groups of these cells which were free of fat droplets, and here they exhibit a more definite epithelial-like structure. Mitotic figures were not seen in this section.

Sections taken through the anatomical position of the funiculus revealed a dense fibromuscular stroma with a suggestion of small atrophic tubules in occasional areas. The lining of these tubules was composed of a flattened epithelium and a fairly thick-walled stroma.

None of the sections taken showed any evidence of ovarian tissue.

The postoperative hormone studies by Dr. Barnes were as follows: 2.6 mg. androsterone and 10 gamma of female sex hormone in a twenty-four-hour specimen of urine.

In a recent interview, the patient stated that the dyspareunia was less marked; that her sex appetite did not seem to be affected one way or the other by the operation, but that she believed she had been more jealous of her husband than formerly. Her weight had remained stationary. She seemed particularly to regret not being able to have children and inquired about the advisability of adopting a child.

CASE 2.—N. S., aged 3, sex undetermined. The following history was given by the mother. Until the age of six months no abnormalities were noted. The child's growth rate, teething, activity, etc., were normal. At about this time, however, the

when the testicles were removed by surgery, developed very severe signs of menopause which proved resistance against female hormones but disappeared when male hormones were applied.

The first case of Dr. Carlisle is not only an intersex but a severe type of developmental deficiency, since the products of the Müllerian ducts are missing. The lack of pubic and axillary hair also is a developmental deficiency, since pubic and axillary hair belong to both sexes. The second case belongs to the very small group of primarily male and secondarily female intersexes. For this case it is very difficult to figure out the rotation point. It seems that there is a possibility of a rotation, an incomplete turning back to the primary sex for a short spell, and again another rotation, which would explain the combination of sex characters that cannot be explained by one rotation point only.

SOME OBSERVATIONS ON THE INFECTIOUS AGENTS CAUSING LEUCORRHEA DURING THE CHILDBEARING PERIOD

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FROM a study of 1,975 patients examined during a venereal disease survey in Tallahatchie County, Mississippi, in 1937, 399, or 20.2 per cent, gave leucorrhea as a chief symptom. Three hundred and eighteen of these women were in the childbearing age and 81 had passed the menopause. The laboratory study of these cases forms the basis for this report.

Leucorrhea in varying degrees is such a common finding in adults that many women think of it as being a normal condition. This attitude on the part of the patient has been supported to some extent by the general practitioner who, too often after excluding cervical lacerations or uterine malposition, thinks of only one infectious etiologic agent, gonococcus. In patients showing leucorrhea, the laboratory diagnosis consists chiefly of a dried urethral or cervical smear stained by the Gram stain method or methylene blue. It should be remembered that such smears are not ideal for a scientific diagnosis of leucorrhea due to *Trichomonas vaginalis*, a protozoan or *Monilia albicans*, a member of the Hyphomycetes order.

LABORATORY DIFFERENTIAL DIAGNOSIS OF INFECTIOUS LEUCORRHEA

There are several infectious agents which should be considered in patients who present the symptom of leucorrhea as a primary complaint during the childbearing age:

1. *Neisseria gonorrhoeae*.—A dried, stained, smear from the cervix or urethra will show gram-negative extra- and intracellular diplococci. In doubtful cases, a culture of the cervical or urethral pus on a chocolate blood agar plate will give the positive test of Gordon and McLeod.¹

2. *Trichomonas vaginalis*.—A suspension of the fresh pus in isotonic magnesium sulphate, when examined under the microscope with the low or high power lens, will show the very active flagellate, which is about the size of a leucocyte.

In several instances in which the operation was done in infancy, the problem of follow-up dilatations was irksome to the patient, family, and attending physician. Having in mind the influence of estrogenic substance on vaginal hypertrophy, it is our plan to do the plastic operation after the onset of puberty.

SUMMARY

Two cases are presented: One a wife with a right testicular-like gonad, a Müllerian duct agenesis, normal external genitalia, and a peculiar absence of body hair. The other case is that of a girl aged three years with a penislike phallus, normal female internal genitalia, and masculinized external genitalia. With the advancing knowledge of endocrinology, genetics, and embryology, it is hoped that these individuals with indefinite sex may be afforded a better opportunity for physical and psychic adjustment to the social scheme.

6 NORTH MICHIGAN AVENUE

DISCUSSION

DR. WALTER SCHILLER.—Up to twenty years ago we had no embryogenetic explanation for the various malformations of genital organs presenting characters of both sexes in one individual, and consequently had no logical system of classification.

Kermauner, who wrote an extensive monograph on the subject, pointed out that these monsters have a combination of male and female sex characters which are assembled without rhyme or reason and thus make a logical explanation impossible. This negativistic attitude of pathologists has changed since Moszkowicz, of Vienna, published his papers on human intersexes. His work is founded on the discoveries of Goldschmidt, of Berlin, which were carried out on butterflies. Moszkowicz most successfully applied Goldschmidt's theories in the field of human pathology. The main point is that sex is determined by chromosomes at the time of fertilization of the ovum. In normal individuals by predominance of one or the other type of sex chromosomes, the sex is fixed and determined in one direction and consequently the primarily ambiguous, "anlage" of sexual organs and characters develop during embryonic life, in one direction. In abnormal cases, the primarily predominant and determining chromosomes lose their power and the chromosomes of the opposite sex succeed in determining power. This occurs at a time called rotation point. Each hermaphrodite, or as we prefer to say, intersex, is sufficiently characterized by its primary sex and the time of the rotation point within the period of the embryonic life. Moszkowicz has published detailed diagrams, demonstrating normal developing of sexual organs and characters for each month of intrauterine life. Comparing the findings of the individual intersexes to these diagrams, it is very simple to determine the primary and the secondary sex, as well as the date of the rotation. Instead of the complicated and vague descriptions of former times, today we are characterizing an intersex by two statements only; first, of what sex was the individual primarily, second, when did the rotation in the secondary sex occur?

Goldschmidt, in his papers, insists that human intersexes all are primarily female and secondarily male. During the last few years we have seen a few cases that disprove this statement, being examples of the primary male and secondarily female type. There is, however, no doubt that the majority of the human intersexes are as Goldschmidt has said, primarily female and secondarily male. The most common type are individuals that are of female appearance, with well-developed female secondary sex characters and female sex feelings. Genitalia present a well-developed female vulva, a short, poorly developed vagina, poorly developed uterus and tubes, and instead of ovaries, testicles of almost normal size, situated in the labia majora. It is very likely that such individuals are not only abnormalities in the anatomic, but abnormalities in the hormonal sense, also. Their sexual life and feelings are female but supported by male hormones. Some of these individuals,

AN EVALUATION OF THE ANTERIOR PITUITARY-LIKE SUBSTANCE INTRADERMAL TEST FOR PREGNANCY

WITH A STUDY OF THE POSSIBLE RELATION OF THIS TEST
TO PROLACTIN CONTENT

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VERY soon after Gilfillen and Gregg¹ described their "new, rapid, economical test for pregnancy and gynecological conditions," this study was undertaken. That this test is not entirely new has already been pointed out by the *Journal of the American Medical Association*.² The test was first proposed in 1929 by Porges and Pollatschek³ of Vienna who subsequently reported the test as not wholly reliable. Alfred Deutsch⁴ in 1929 and Hyman Strauss⁵ in 1930 also reported the test as unreliable after their investigations. Weisman and Yerbury⁶ recently came to the same conclusion. Huberman, Israeloff and Hymowitz⁷ reported in their paper read at the American Medical Association Convention in Atlantic City in June, 1937, that the test was accurate in 95 per cent of the pregnant women. They used "follutein" as an antigen in performing the intradermal test. They do not offer this test as a substitute for other tests but as a simple aid in the diagnosis of the gravid state. Schneider and A. E. Cohen,⁸ however, concluded that the results obtained with antuitrin-S injected intradermally in no way exhibit the reliability of this test as a means of diagnosing pregnancy or gynecologic disorders. The present authors' controlled studies upon a large group of patients completely justify the statement in the *Journal of the American Medical Association*, "There is, as yet, no reason to believe that the test is any more reliable now than it was in 1929."

The test as performed by Gilfillen and Gregg was duplicated exactly. This consisted of the intradermal injection of two minims of fresh anterior pituitary-like substance from pregnancy urine which had been kept on ice. Readings were taken at the end of one-half hour and at the end of one hour. A failure of the skin to react was read as positive for pregnancy. An increase in the size of the wheal above 7 mm. in diameter with a surrounding erythema was read as negative for pregnancy. The test material used had an "expiration" date that was a minimum of four to five months after its use.

Eighty-eight pregnant women were used in the first part of the study. These women all attended the Prenatal Out-Patient Clinic of the Coney Island Hospital and were pregnant two or more months. Table 1 summarizes the readings and results in this group.

Of these 88 women, 8 gave a nonpregnancy reading; 80 gave a pregnancy reading.

In the second part of the study 41 women were used. These included patients on the wards of the hospital and female technicians in the laboratory. One of these

3. *Hemophilus Ducreyi* Causing Ulcerations of the Cervix or Vaginal Wall.—A culture of the pus, streaked on a chocolate blood agar plate, shows slightly hemolytic white colonies of about 0.25 mm. in diameter after twenty-four hours incubation at 37.5° C. Phenol toluidine blue stain from these colonies shows small diplobacilli of 1.5 by 0.5 microns. They are gram-negative. The Dmelcos' skin test is positive.

4. *Monilia albicans*.—A suspension of the fresh pus in 10 per cent NaOH, when examined under the microscope with the low or high power lens, shows the characteristic budding. A stab culture of the fresh pus inoculated into a tube of gelatin and cultured at room temperature will show the characteristic "inverted pine-tree" growth in ninety-six hours.

5. *Various Streptococci and Staphylococci*.—The Gram stain made from the pus will show the presence of these organisms. A streak on a blood agar plate with subculture to gelatin will complete the identification.

6. *Corynebacteria*.—A direct smear stained with methylene blue and by the Gram stain method will show the characteristic organisms. A culture on Loeffler's serum agar, after 18 hours growth at 37.5° C., and stained by the same method as the direct smear, will confirm the diagnosis.

7. *Vincent's Spirillum*.—A direct smear stained with the Gram method will show the characteristic organisms. One must always keep in mind the frequent occurrence of nonpathogenic spirochetes and the presence of the Döderlein bacillus in the vagina.

PROCEDURE

A. Direct smears were made from the cervix and urethra and stained by the methylene blue and the Gram-staining techniques. The cervical smears were taken after insertion of a vaginal speculum.

B. Hanging drop wet preparations were made from the same fresh material by suspending it in isotonic magnesium sulphate solution and 10 per cent NaOH, and were studied for *Trichomonas vaginalis* and *Monilia albicans*.

FINDINGS

TABLE I. THE FINDINGS FROM LABORATORY EXAMINATION OF URETHRAL OR CERVICAL PUS FROM 318 LEUCORRHEA PATIENTS BETWEEN THE AGES OF 15 AND 44 YEARS

NAME OF ORGANISM	NUMBER POSITIVE	PERCENTAGE POSITIVE
Gonococci	181	56.9
Staphylococci	84	26.4
<i>Trichomonas vaginalis</i>	57	17.9
Streptococci	36	11.3
<i>Monilia albicans</i>	10	3.1
<i>Hemophilus ducreyi</i>	6	1.9
<i>Vincent's spirillum</i>	3	0.9
<i>Enterobius vermicularis</i>	2	0.6

There were 35 patients showing leucorrhea who did not show any of the organisms listed in Table I. They showed one or more of the following miscellaneous organisms: *Bact. coli*, micrococci, Saprophytic spirochetes and mycobacteria; Vibrio, Enterococci, Bacterioides, and the Döderlein bacillus.

Of the 318 leucorrhea patients, 6, or 1.9 per cent, gave a positive Frei test.

Various members of the miscellaneous group of organisms also appeared from time to time in the pus containing the other more pathogenic organisms listed in Table I. In some cases, more than one pathogenic organism was found in the same patient. In general, gonococci were not found in pus containing a large number of the trichomonas, or monilia or Döderlein bacilli. There is an apparent antagonism between

them. The relative incidences of streptococci and staphylococci were greatest in those cases that gave a history of abortion or miscarriages within the last year. In some cases, under the miscellaneous group, there was a history of repeated use of concentrated chemical douches which should be considered in the etiology.

TABLE II. FINDINGS FROM LABORATORY EXAMINATION OF URETHRAL OR CERVICAL PUS FROM 81 PATIENTS OVER FIFTY YEARS OF AGE (AFTER THE MENOPAUSE)

NAME OF ORGANISM	NO. POSITIVE	PERCENTAGE POSITIVE
<i>Trichomonas vaginalis</i>	47	58.0
Gonococci	10	12.3
<i>Monilia albicans</i>	9	11.1

The miscellaneous group was not worked out in this series.

TREATMENT

Table III shows the laboratory results from the uses of sulfanilamide in the treatment of 176 cases of gonorrhea in women without the presence of *Trichomonas vaginalis*, 25 cases showing both the gonococcus and the trichomonas, and 79 cases of *Trichomonas vaginalis* infection without the presence of gonococci.

TABLE III

NO. CASES AND LAB. FINDINGS BEFORE BEGINNING THERAPY	AM'T. OF SULFANILAMIDE GIVEN BY MOUTH IN 8 DAYS	LAB. FINDINGS 2 WK. AFTER BEGINNING TREATMENT			
		NO. POS. FOR G.C.	% POS. FOR G.C.	NO. POS. FOR TRI-CHOMONAS	% POS. FOR TRI-CHOMONAS
176 Positive for gonococci	240 gr.	46	25.9	0	0
25 Positive for both gonococci and <i>Trichomonas vaginalis</i>	240 gr.	20	80.0	24	96
79 Positive for <i>Trichomonas vaginalis</i>	240 gr.	0	0.0	75	95

The sulfanilamide was given in doses of 10 gr. four times per day, for the first four days; and 5 gr. 4 times per day for the next four days. No other therapy was given. When the check up was made two weeks after beginning the therapy, not only was there a marked drop in the number of positive smears by laboratory study, but the leucorrhea symptoms were markedly improved. In the *Trichomonas vaginalis* group, there was very little noticeable improvement. These cases, however, showed rapid improvement when put on vaginal douches, with acetylaminohydroryphenylarsenic acid (Devegan) every night for a week before, and just after a menstrual period. In the cases where gonococci and *Trichomonas vaginalis* were both present, the sulfanilamide therapy was combined with the douches with good effects. A few patients did not return for the check up, or were menstruating at the time of the check up and do not appear in the final analysis. Many of the more resistant cases were chronic salpingitides.

CONCLUSION

The frequency with which nongonococcal organisms appear in cases of infectious leucorrhea warrants at least an examination by microscope and culture if necessary for *Trichomonas vaginalis* and *Monilia albicans*. This is especially important where one is going to use sulfanilamide therapy. Sulfanilamide therapy is most effective when used in acute cases of gonorrhea, and has no significant effect on leucorrhea due to *Trichomonas vaginalis*. There is an apparent antagonism between *Trichomonas vaginalis*, *Monilia albicans*, and Döderlein bacilli against the gonococcus in vivo.

REFERENCE

- (1) Gordon, J., and McLeod, J. W.: J. Path. & Bact. 31: 185, 1928.

A CASE OF ACEPHALUS HOLOACARDIUS*

HENRY BUXBAUM, M.D., AND DAVID V. WACHSMAN, M.D., CHICAGO, ILL.

(From the Service of the Chicago Maternity Center)

THIS case of a parasitic monster is reported because of the rarity of its occurrence. There have been 20 similar cases reported under different designations, which would seem to infer a definite need for a standardization of nomenclature in attempts to describe different types of fetal abnormalities. Monsters resembling ours have been called amorphous acephalus, acardiacus acephalus, and, better still, acephalus holoacardius, which is more descriptive of the case herein reported.

The patient was a white, 21-year-old gravida iii. Her family history was essentially negative with no record of any multiple pregnancies or monstrosities in either her or her husband's antecedents. She had the usual diseases of childhood with no serious ailments or operations since. Her menstrual history was normal; onset at the age of ten years, twenty-eight-day type of five days' duration. The last menstrual period started on June 18, 1937, and the estimated date of confinement was March 27, 1938. Her previous obstetric history revealed two previous pregnancies, both terminating spontaneously in two normal living children. Her present pregnancy was uneventful; blood pressure and urinalysis were always normal, and she had no serious complaints throughout her prenatal period. Weight gain was slight: from 67.7 to 69.5 kilograms. Labor started March 21, 1938, at 2:30 A.M. The first and second stages proceeded rapidly, lasting forty-five minutes, and she was delivered in her own home on the out-patient service of the Chicago Maternity Center at 3:15 A.M. of a normal living female child, weighing 3,720 gm. Ten minutes later the placenta, found to be detached, was delivered by simple expression. Estimated amount of blood loss was 250 c.c. Attached to the fetal surface of the placenta was an irregular mass enclosed in an intact amniotic sac, containing about 20 c.c. of clear liquor amnii (Fig. 1). The patient's condition was good; no anesthetic was required, and she had an uneventful puerperium, getting out of bed on the eighth day and was discharged as well with her normal baby on the fourteenth day.

Description of Specimen.—The placenta was intact, measured 18 by 20 by 3 cm. and weighed 720 gm. The maternal surface was normal but on the fetal surface was the globular mass shown in Fig. 1, enclosed in its intact amniotic sac. Upon rupture of the sac the monster shown in Fig. 2 was found attached to an umbilical cord, measuring 16 cm., which was attached to the fetal surface of the placenta about 8 cm. from the attachment of the cord of the normal infant. There was definitely one placenta, one chorion, and two separate amnions. This monster measured 12 by 12 by 8 cm. and weighed 1,320 gm. It consisted of two well-

*Read at a meeting of the Chicago Gynecological Society, April 15, 1938.



Fig. 1.



Fig. 2.

developed thighs and two legs ending in feet with two toes on each foot. Both feet were of a talipes equinovarus. The top of the mass was round and smooth, and the whole thing was covered with a pink, healthy-looking epidermis. Between and a little above the thighs on the anterior wall was a structure closely resembling a penis with a dimple below the tip that resembled a urethra. The cord was inserted at the base of the left thigh. The circulation in the monster appeared good. Fig. 3 is an x-ray picture of the monster and shows a pelvic girdle, two femurs, two tibiae, one fibula, and a few metatarsal bones on one side.

DISCUSSION

This case is interesting from several standpoints. In the first place, although this is definitely monozygotic twins, one of the babies is a female and the other one apparently a male. Also the origin of the circulation in the monster is a matter of conjecture. Inasmuch as no heart is evident in the monster, its blood supply must

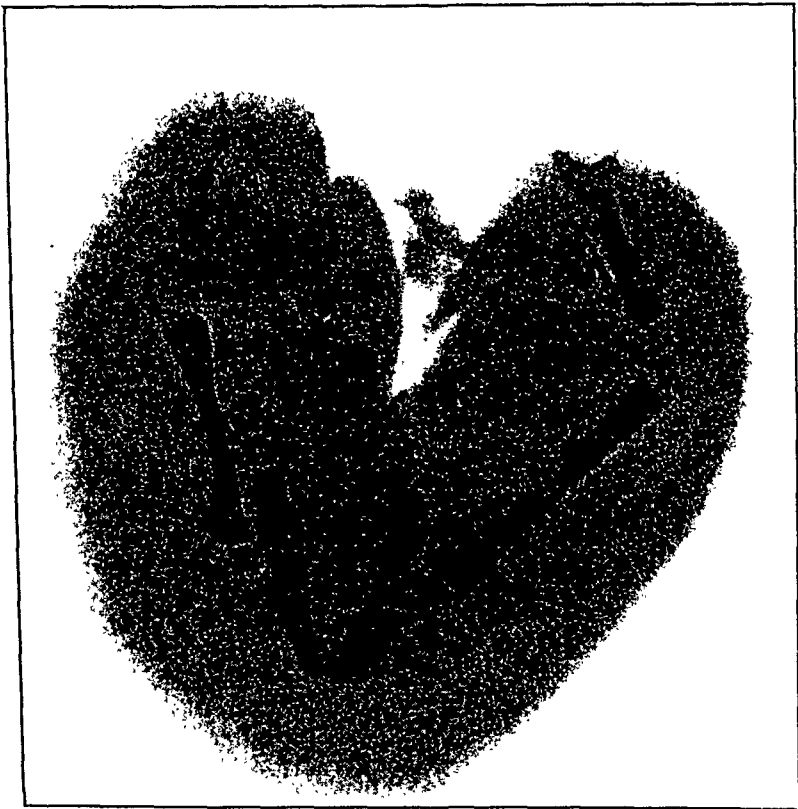


Fig. 3.

have come from the normal baby via an anastomosis of blood vessels in the placenta, and even if an embryonic heart originally existed in the monster, it had no doubt been overcome, then superseded by the heart of the healthy baby, with resulting atrophy and complete disappearance, a conclusion not altogether illogical. Therefore, this was not only a monster but a parasite as well. It is interesting to note at this time that the well baby revealed no cardiac hypertrophy on physical and radiologic examination.

Inasmuch as the cause of these peculiarities in embryology is still a controversial topic, one hesitates to venture an opinion whether hereditary or environmental factors are responsible but from the facts presented in this particular case, one may be justified in assuming that environment was the sole factor involved, on the basis that here is a uniovular twin in which one baby, getting more than its share of nourishment, completely overcomes and dominates the nutrition of the weaker baby which ceases to develop and becomes a parasite, depending for its maintenance upon the healthy baby.

PRIMARY CANCER OF THE VAGINA*

FREDERICK V. EMMERT, M.D., F.A.C.S., St. Louis, Mo.

(From The Barnard Free Skin and Cancer Hospital)

PRIMARY carcinoma of the vagina is not common. Of all cancers, in women, it occurs in less than 1 per cent, while in genital cancer, it occurs in 2.7 per cent (Taussig).

I have investigated the material at The Barnard Free Skin and Cancer Hospital and found 30 cases of primary carcinoma of the vagina. During the same twenty years, we have seen 1,546 cases of genital cancer, so that the incidence is 1.09 per cent. It is hardly necessary to point out that secondary carcinoma of the vagina has been excluded. To these 30 cases, I have added 4 cases from the private practice of Dr. Taussig, and 3 from that of the late Dr. Gellhorn. The following study, therefore, is based on 37 cases of primary cancer of the vagina.

As to the age of the patients, the youngest was 26, the oldest 82. The majority were between 45 and 60 years, the average being 53. This corresponds fairly well with other statements in literature. In 1930, Baldwin could collect but 3 cases in patients less than 20 years of age with cancer of the vagina.

Concerning the location, all authors agree that primary carcinoma develops in the posterior fornix most frequently. In our 37 cases, this was found to be true 14 times; 5 originated in the anterior wall; 13 were located on the lateral walls and 6 were annular in shape. Rohde found of 123 cases, 71 on the posterior wall, 23 on the anterior wall, 13 on the lateral wall, and 16 of the ring-type encircling the vagina.

Previous labors seem to have very little to do with the etiology, for out of 37 cases, there were 7 nulliparous women. Moreover, if parity had any influence, primary carcinoma should be much more common.

Cancer of the vagina is either ulcerative or papillary in type and occurs in single and less often multiple lesions. In our cases, 24 lesions were single and 13 multiple, 26 being nodular, and 11 ulcerative. Microscopically, cancer in this location is of the squamous cell type. In 30 cases in which we have definite data, we found this to be the case in 29. The remaining case, which is from Dr. Gellhorn's private practice, was one of adenocarcinoma in a young woman of 27 years.

The histologic grade was determined on the basis of cellular differentiation of the specimen according to the method of Broders. All tissues available at this time are squamous cell carcinoma, and of these 13 cases studied, 8 were Grade II, and 5 were Grade III. This is too small a series from which to deduce any factors of significance as to any specific features of the histology of vaginal carcinoma. Thus, none were of the markedly highly differentiated or undifferentiated types.

*Read before the St. Louis Gynecological Society, January 11, 1935.

In our 37 patients, 31 had hemorrhage, one noticed slight bloody discharge after intercourse, the remaining 5 did not remember any such symptoms.

Of the 37 patients of our series, the first 4 were treated purely palliatively with acetone, because their condition was far too advanced for any hope of cure. Seven patients received no treatment or were treated elsewhere and cannot be considered in this connection. Of the remaining 26, 21 were treated with radium applied in various forms. From these 21, 2 must be deducted because lacking follow-up. Of the 19, 4 are still alive, namely 11, 8, 7, and 1 years, respectively, after treatment. Five patients were subjected to radical vaginal colpectomy and hysterectomy, with one postoperative death 5 days later. Of the remaining 4, 2 are alive and well, 6½ and 1½ years, respectively, after operation. A third case is alive but with recurrence. The one remaining patient died 3 years after operation.

If we may draw conclusions from a limited material, and from an experience extending over 20 years, we must admit that the hopes based on operation and radium therapy have not yet been fulfilled. Out of 33 cases treated over five years ago, only four remained well, three following radiation, one following operation, an absolute curability of 12 per cent. Considering only those cases that were treated with radium or by operation, we have a total of 26 cases with five-year cures in four, making a salvage of 15 per cent. It must be admitted that the radical operation undertaken in the five cases is quite different from the simple surgical excision and requires a degree of technical skill, since the paravaginal tissues and practically the entire vagina must be removed.

The problem, therefore, is still in abeyance. The suggestion I wish to make tentatively at this moment is this, that in the early stages a really radical operation be performed and radium with or without x-rays be applied in more advanced cases of primary carcinoma of the vagina.

METROPOLITAN BUILDING

Benthin, W.: Genital Disease in the Menopause, Med. Klin. 34: 605, 1938.

Among 565 women in the menopause Benthin found that 244 (44 per cent) complained of bleeding, 139 (25 per cent) had descensus and prolapse of the uterus, 77 (13.9 per cent) had an ovarian tumor, 7 (1.2 per cent) had uterine fibroids, 15 (2.6 per cent) had other genital ailments, 42 (7.7 per cent) had bladder symptoms, 23 (4.1 per cent) had intestinal ailments, and 18 (3.2 per cent) had nongynecologic conditions.

Among the 244 bleeding cases 114 (46 per cent) were of benign origin and 130 (54 per cent) were from malignant disease. Among the 77 ovarian tumors, carcinoma was present in 39 cases (50 per cent).

It is interesting to observe that inflammatory disease, which forms 90 per cent of the ailments of women in the reproductive years, was almost completely absent in the menopause. Likewise endocrine disturbances other than menopausal symptoms played no role.

J. P. GREENHILL.

LIVER PRESENTATION*

REPORT OF TWO CASES

EDWARD ALLEN, M.D., CHICAGO, ILL.

STANDARD textbooks of obstetrics do not mention presentation of a baby by its liver. Because of the apparent infrequency and difficulties arising in differential diagnosis, it would seem that a report of two such cases might be of interest.

CASE 1.—Mrs. L. C. S., aged 20 years, primipara, had her last menstrual period April 7, 1932. Pregnancy progressed normally until September 16, when she reported to the clinic stating she had passed 5 to 10 drops of bright red blood from the vagina two days previously. No evidence of bleeding was found and the resident in obstetrics instructed her to return in two weeks. On September 18 she again reported to the clinic, saying that the night before she had suddenly lost about one quart of clear fluid from the vagina. No fluid could be seen coming from the vagina and on rectal examination the cervix was noted as firm, long, and not dilated. She was sent home to remain in bed for twenty-four hours. At her next visit on September 30 she stated that small quantities of fluid which she did not believe was urine still escaped from the vagina. Fetal heart tones at this time were normal. The same complaint and findings were again noted on October 10. On November 18 the patient returned, complaining of backache and abdominal tenderness. At this time the fundus of the uterus was 28½ cm. above the symphysis, ballotable head in the fundus and heart tones were heard in the upper quadrants. Rectal examination did not reveal any change from previous examinations.

On the morning of November 28 the patient was admitted at 8 A.M., stating that bleeding had begun at 6:30 A.M. and was still present; she believed she had lost about a cupful of blood. Slight pains began at 7 A.M. and were continuing. Fetal heart tones were not heard but fetal movement was felt by the mother and the examiner. No rectal examination was made. The blood pressure was 124/80 and the hemoglobin 55 per cent. The discharge from the vagina seemed to be blood-tinged amniotic fluid. The patient's condition remained the same until 2:30 P.M., when pains began every five to seven minutes, lasting twenty to thirty seconds. There was no increase in the bleeding. At 4 P.M. ¼ gr. of morphine sulphate was administered. At 11:30 P.M. there was a sudden increase in the vaginal bleeding and pulse had risen to 120. The patient stated definitely that she felt fetal movement although the heart tones could not be heard. Her husband was typed for a blood transfusion.

When I saw the patient for the first time at 1:30 A.M. there was a steady trickle of bright red blood from the vagina. The maternal pulse rate had risen to 136; blood pressure was 140/88 and temperature 99.2° F. No fetal heart tones could be heard. Vaginal examination revealed a soft boggy mass completely filling the cervix which later was found to be the fetal liver. The cervix was about two-thirds dilated. Brisk bleeding accompanied the examination. On more careful examination it was found that two fingers could be slipped by the mass and the examining fingers seemed to meet the unruptured bag of waters. These were ruptured and a large amount of clear straw-colored fluid escaped. On further introduction of the hand into the uterus, difficulty was experienced in feeling fetal parts, which we later found was due to the fact that the hand had been introduced directly into the abdominal cavity of the fetus. Further manipulation allowed us to grasp both feet which were drawn gently through the cervix. Constant traction was maintained, and at 2:15 A.M. a six-pound dead fetus was delivered. The placenta delivered normally a few moments later.

*Presented at a meeting of the Chicago Gynecological Society, Clinical Meeting, April 15, 1938.

Examination of the fetus revealed an almost total absence of the anterior abdominal wall with the liver protruding through it still oozing blood from cracks in its capsule. The bladder had been ruptured and was collapsed. Both anus and urethra were imperforated.

CASE 2.—Mrs. D. H., aged 26 years, had had three normal full-term children, in 1927, 1929, and 1931, respectively. The last menstrual period was Sept. 6, 1933. The patient had attended the cardiac clinic because of a mitral stenosis, but the heart was well compensated. The blood pressure had varied between 110/70 and 120/70, and the urine did not contain albumin or sugar. Labor pains began at home at 7:30 A.M., May 11, 1934. At 12 o'clock the membranes ruptured spontaneously. The patient was examined by the resident on the out-patient service at 5:30 P.M., and a diagnosis made of right sacrum anterior and probable placenta previa. At this time the patient was bleeding steadily from the vagina. The pulse rate was 120, irregular and weak. The fetal heart tones were 120 in the left lower quadrant. Immediate transfer to the hospital was ordered.

Upon arrival at the hospital the fetal heart had slowed to 80 beats per minute and before the patient could be prepared for vaginal examination they had ceased. Six per cent glucose solution was started at once intravenously as the vaginal bleeding was more pronounced and the maternal pulse had risen to 160. Vaginal examination revealed a rather firm mass filling the almost completely dilated cervix. Rather profuse bright red bleeding was produced by the examination. Inspection of this mass by means of vaginal retractors showed the smooth capsule of the liver broken here and there by fissures from which considerable blood was flowing. Under deep anesthesia the liver was gently replaced in the uterus, both feet were grasped and brought into the vagina. Delivery of the body was accomplished easily, but there was insufficient dilatation of the cervix to permit passage of the rather large after-coming head. Perforation of the skull was accomplished by slipping the anterior lip of the cervix forward and entering the cranial cavity at the base of the skull. The placenta was expressed, leaving a small piece in the uterine cavity, which was removed manually. Blood transfusion was not given although a compatible donor was present. Hemoglobin was 78 per cent. The patient left the delivery room in fair condition. Puerperium was uneventful.

The fetus weighed 5 pounds. The absence of the anterior wall permitted exstrophy of almost all the abdominal organs. There was a rather large spina bifida.

SUMMARY

Two cases of liver presentation are described, illustrating the need for care in the diagnosis of central placenta previa in the last trimester of pregnancy. Cesarean section in most clinics is the accepted treatment for the central variety of placenta previa. Gross fetal abnormalities which are not demonstrable by roentgenography may produce the clinical picture and vaginal findings of central previa and should be considered in the differential diagnosis.

55 E. WASHINGTON STREET

Martines, S.: *The Content and Elimination of Iron in Breast Milk*, Riv. Ital. di ginec. 20: 467, 1937.

The author found that the iron content of breast milk is 2.7 mg. per liter, is greater than in colostrum, and is independent of the intake of food. The milk of multiparas is richer in iron than that of primiparas.

In a group of lactating mothers, placed on iron therapy, a remarkable increase in iron was noted in the milk.

The author highly recommends the administration of iron during lactation, especially when anemia is present.

AUGUST F. DARO.

SARCOMA OF THE UTERUS*

WITH REPORT OF THREE CASES

W. C. DANFORTH, M.D., EVANSTON, ILL.

SINCE the month of June, 1936, three patients with sarcoma of the uterus have appeared in our service. As it had been some years since we had seen a case, it seemed of interest that these three should be seen within a limited time. Sarcoma of the uterus has been regarded as a fairly rare tumor. Some years ago Evans estimated, after studying a considerable number of cases, that sarcoma appeared about once in 40 cases of malignant tumor of the uterus. In view of the short time in which these three patients were seen it may be fair to inquire whether a more thoroughgoing study of pathologic material might not show a greater incidence than we have hitherto assumed. During the period covered by this report there were 178 myomas of the uterus. In 123 of these the myoma was the primary reason for treatment and in 51 it was of secondary importance. In 4 cases the myoma was in the cervix. The incidence of sarcoma as compared with myoma was one to 59. During the same period there were 25 carcinomas of the uterus, of which 15 were of the cervix and 10 were corporeal. During this brief period, therefore, the frequency of sarcoma as compared to cancer was one to 8.33. This incidence is higher than we heretofore believed and cannot be regarded as authoritative because of the small number of cases. Preoperative diagnosis of sarcoma is difficult to make. In all of these cases the diagnosis was first made in the laboratory. The rather characteristic appearance of the gross cut surface may give reason to suspect sarcoma.

The case histories in brief are as follows:

CASE 1.—June 20, 1936. Patient, aged 39 years. Referred by Dr. J. G. Carr. She complained of low backache and pain in the left lower abdomen. Her last period had been profuse. Examination showed an ovoid mass on the left side as large as a coconut. Operation disclosed an endometriotic cyst on the right side and a spherical fibroid tumor of the uterus. On the left side was a smaller endometriotic cyst.

Extract from pathologic report: "A very cellular sarcoma in the wall of the uterus, growing beyond the limits of encapsulation of the fibroma in which it arises with large hyperchromic, many shaped nuclei. Mitotic figures are very rare, but the tumor is definitely malignant and invasive."

CASE 2.—July 15, 1937. A woman of 47 years. Referred by Dr. Arthur Colwell because of bleeding apparently caused by a large fibroid. Steady though not profuse bleeding had gone on for three weeks prior to admission to the hospital. Subtotal hysterectomy was done. Recovery was uneventful. The pathologic report was as follows (extract from pathologic report):

"The huge tumor is composed of pleomorphic cells with irregular vesicular round basophilic nuclei and eosinophilic cytoplasm. Some of the cells are round, others are narrow, elongated with a fibrillar structure. Marked irregularity in size, shape, contour, and staining affinities are present. In some field retrogressive changes

*Read at a meeting of the Chicago Gynecological Society, April 15, 1938.

TABLE I. RESULTS OF SKIN TESTS IN PREGNANT WOMEN

NUMBER OF CASES	LENGTH OF PREGNANCY IN MONTHS	NUMBER OF PREGNANCY REACTIONS	NUMBER OF NON-PREGNANCY REACTIONS
6	2	4	2
6	3	6	0
18	4	16	2
12	5	12	0
15	6	13	2
17	7	16	1
11	8	10	1
3	9	3	0

women was admitted to the hospital for a threatened abortion. She was approximately fifteen weeks pregnant and was expected to give a positive pregnancy reading but did not. After several days in bed, she was discharged as still pregnant. Of the remaining 40 women, 27 gave a positive pregnancy reading; 13 gave a negative pregnancy reading.

During pregnancy the prolان content of the body increases. The findings of an increased prolان in the female may mean pregnancy. In view of the unexpected high number of positive pregnancy readings obtained in the nonpregnant group of women, it was decided to study the possible relationship of these findings to prolان content.

Ten nonpregnant women who gave a definitely positive pregnancy reading were selected for prolان determinations. These determinations were done using a modification of Zondek's method for the extraction and assay of follicle stimulating hormone (Prolان "A") from the urine.⁹ Microscopic examinations of the ovaries from the autopsied mice was done in all cases as a check on the gross diagnosis of positive or negative prolان. Of the 10 women selected for these prolان studies, all showed negative prolان readings, indicating no increase in their prolان excretions in the urine.

TABLE II. PROLAN STUDIES IN NONPREGNANT WOMEN AND IN MEN WITH POSITIVE SKIN TESTS

	NO. STUDIED FOR PROLAN	PROLAN NEGATIVE	PROLAN POSITIVE
Nonpregnant women with positive pregnancy skin test	10	10	0
Men with positive pregnancy skin test	6	5	1

Increased prolان may be found in such conditions as early menopause, hyperthyroidism, incomplete abortion, chorioepithelioma, follicular cystosis of the ovary, persistent corpus luteum cyst of the ovary, testicular atrophy, removal of the testicles, over-secretion of the pituitary gland as in gigantism, acromegaly, etc., pregnancy, and following bilateral oophorectomy. If any of these conditions were present they were not marked by an increased prolان. The mechanism of this "intradermal test for pregnancy" is not entirely clear. It does not seem to be related to either pregnancy or to prolان content of the body.

GRANULOSA CELL TUMOR OF THE OVARY WITH A CARCINOMA OF THE BREAST

RITA S. FINKLER, M.D., NEWARK, N. J.

*(From the Surgical and Gynecological Services and Division of Laboratories,
Newark Beth Israel Hospital)*

A 37-year-old married, white female was admitted to the Surgical Service of the Newark Beth Israel Hospital on May 19, 1936, for the removal of a large uterine fibroid. For the past six months she had complained of an increasing sense of pressure over the bladder and rectum. The menstrual history was normal; onset at the age of 12, occurring every twenty-eight days and lasting four or five days. There had been no increase in the frequency or the amount of flow. The last period occurred three weeks prior to admission. She was married and had one living child. There was no history of any other pregnancy. The past history is irrelevant, and the family history is negative, except that her mother had diabetes. The routine urinalysis showed 2.5 per cent glucose, and the blood sugar was 273 mg. per 100 c.c. of blood. A diagnosis of diabetes mellitus was made. The patient was temporarily discharged to be treated at home for her diabetic state.

She was readmitted on June 7, 1936. The pelvic examination revealed the uterus to be enlarged to about the size of a three and one-half to four months' pregnancy. A cystocele and a lacerated cervix were also found. The physical examination was otherwise essentially negative. On palpation of the breasts, no masses were felt, and there was no tenderness.

She was operated upon on the following day. At the operation a large uterus studded with many fibroids, and a right cystic ovary were found. The appendix was constricted at two points. A hysterectomy, right oophorectomy, and appendectomy were performed.

Summary of Pathologic Examination.—*Gross:* Specimen consisted of a supra-cervically amputated uterus, without tubes or ovaries. It was ovoid in shape and measured approximately 10 cm. in diameter. In the wall and beneath the serosa, were many circumscribed nodules ranging from 2 cm. to 5 cm. in diameter. They were all composed of whorls of dense gray tissue, with occasional pinkish, more cellular areas between them. The endometrium was congested. Received separately, was an ovary, 5 cm. in diameter. It contained a large cyst on whose lining were occasional small roughened excrescences. Besides the large cyst, the ovary contained two nodules. One measured 2½ cm. by 2 cm., composed of yellow, granular tissue, the other measured 1½ cm. in diameter and was composed of grayish, granular tissue. Received separately, was an appendix measuring 7 cm. in length with an average diameter of 4 cm. The lumen was obliterated at the tip.

The microscopic examination of the ovarian tumor revealed for the most part, a uniformly diffuse cellularity. The cells had a scant cytoplasm with uniform, fairly pyknotic, large nuclei. Mitotic figures were scarce. In places, these cells were arranged radially, about a cavity, in which there was eosinophilic material; the formation of these latter structures remotely resembled atypical follicles (Fig. 1). In addition, there were multiple fibromyomas with adenomyosis, a pronounced endometrial hyperplasia, and endometriosis of the appendix.

Following this diagnosis a bio-assay of the urine was carried out on the eighth day following the operation and revealed the presence of only 6 rat units of estrin and 25 mouse units of prolan per liter of urine. Her blood sugar during her stay in the hospital while receiving insulin therapy, varied from 188 mg. to 231 mg. per 100 c.c. of blood. The patient made an uneventful recovery and was discharged twelve days after the operation.

are prominent, in others active growth is demonstrated by numerous mitotic figures. Numerous thin-walled blood vessels are seen surrounded by round and elongated cells attempting to form fasciculae. In such regions of good blood supply, growth is abundant. Necrosis and degeneration occur distant to the blood supply.

“Diagnosis: Intramural fibromyoma with sarcomatous degeneration. Right cystic ovary and oviduct.”

CASE 3.—Sept. 22, 1937. A woman of 62 years had suffered from uterine bleeding for several weeks. About ten days before she was brought to us she passed a spherical mass which was pronounced fibroma uteri in a diagnostic laboratory in Florida. Examination disclosed a large irregular uterus extending to within an inch of the umbilicus. The os was about 2 cm. wide. Subtotal hysterectomy was done, the uterus being opened for inspection immediately. A large tumor mass projected into the uterine cavity. It was greenish gray in color and gave off a foul odor. As it did not resemble an adenocarcinoma, the operation was completed. Cut section of the tumor showed a smooth pale homogeneous surface, softer than the usual fibroid. The pathologic report was as follows (extract from pathological report):

“Microscopic examination of the above described submucous tumor reveals a solid histoid vascular tumor with extensive areas of hemorrhage, degeneration, and necrosis. Groups of anaplastic, irregularly sized hyperchromatic cells are seen associated with numerous thin-walled blood vessels. The anaplastic cells have a large basophilic nucleus irregularly round to oval, containing nucleoli; some are multinucleated. The protoplasm is pale granular pink and varies in amount. Some of the nuclei are naked; others contain variable amount of pink granular protoplasm. Mitotic figures are numerous. Such groups of anaplastic cells imperceptibly merge into the surrounding tissue where they become elongated and slender. Their nuclei become lighter and vesicular, exhibit a definite nuclear membrane and one or two nucleoli. The cytoplasm increases in amount, becomes pink and granular and assumes a fibrillar structure. Here also are seen quite a variation in the size and shape of the nuclei and numerous mitotic figures. In places these cells are growing in a fascicular formation. The large anaplastic cellular areas are supplied by numerous thin-walled blood vessels and it is here that necrosis and hemorrhage is most extensive. Edema is quite pronounced throughout the tumor.

“Diagnosis: Huge solitary pedunculated submucous sarcoma of the uterus. Subacute to chronic left salpingitis with hydrosalpinx. Fibrous adhesions between the left oviduct, the atrophic ovary, and the uterus. Multiple intramural fibromyomas with calcification.”

Knudtson, T. G.: Autotransplantation of the Ovary, *Acta obst. et gynec. Scandinav.* 17: 407, 1937.

The term auto-transplantation refers to the transfer of ovarian tissue from its normal situation to another portion of the body. Homologous iso-transplantation is the transfer of ovarian tissue from one woman to another and homologous allo-transplantation is the transfer of ovarian tissue from an animal to woman. Since hormone therapy of menopausal symptoms is so expensive and so much trouble, the author prefers autotransplantation. Since 1933 he has used this procedure in 16 cases and he has employed the Douay technique. This consists of transplanting pieces of ovary into the labia majora. In 10 women more than one year has elapsed since the operation. Six of these women have had excellent results up to three years. In none of the cases was there any local discomfort or symptoms. Relief from symptoms is not obtained until three months after the transplantation is made. However, it was found that the amount of anterior pituitary hormone in the urine decreases before the hot flashes subside. This indicates that estrin production commences before the hot flashes are relieved.

J. P. GREENHILL.

the appearance of a carcinoma of the breast in a woman of 37 years of age, three months following the removal of a granulosa cell tumor of the ovary, must be considered coincidental until further observations on similar cases can be made.

The adenomyosis and endometriosis which was present in this instance is probably related to the ovarian tumor.

I am indebted to Dr. B. H. Greenfield and Dr. J. Flax from the Surgical Service of the Newark Beth Israel Hospital, through whose courtesy this case was reported, and also to Dr. William Antopol, Director of the Laboratories of the Newark Beth Israel Hospital, Newark, N. J., for his generous assistance in the preparation of this paper, and for the pathologic diagnosis on all tissues herein described.

35 LESLIE STREET

AN UNUSUAL CASE OF PLACENTA ACCRETA DISCOVERED AT CESAREAN SECTION

MILTON G. POTTER, M.D., F.A.C.S., BUFFALO, N. Y.

MATHIEU collected eight cases of this rare condition discovered at cesarean section and cites a ninth case. All of these patients were treated by hysterectomy and recovered. A report of a tenth case, in which it was impossible to remove the uterus, is herein cited.

Patient G. was a primipara, 35 years old, who had been married for twelve years. Her menstrual history had always been normal, in that her periods were regular, lasting approximately five days with no pain. She had a thyroidectomy in 1933. The last period noted before her pregnancy was Aug. 15, 1935 which would make the date of expectancy approximately May 22, 1936.

During the early stage of pregnancy, the patient was miserable, in that she had during the first four months, four acute terrific attacks of lower abdominal pain, which lasted for several days at a time. These attacks were so severe she would faint and could be controlled only with huge doses of morphine. During her last attack in November, 1935, which lasted one week, there was no bowel movement, and all attempts to correct this condition with enemas and cathartics failed, until the patient discovered that cider, by mouth, had the desired but painful effect.

From Jan. 1, 1936, the patient had no more attacks of pain and the family physician reports a normal prenatal period thereafter, with the feeling of life present until May 26, 1936 (four days after her expected time of delivery).

When the patient was one month over term, the family physician became alarmed, sent her into the hospital for induction of labor, which failed. After a stay of one week in the hospital, during which time the x-ray revealed a dead fetus and large uterine tumors, she returned home undelivered.

Another month elapsed (two months beyond her expected time of delivery) when the patient was again returned to the hospital by the family physician, who called for obstetric consultation.

At this time (July 29, 1936) all concerned were alarmed, even though this patient with a large hard abdomen, felt well. Pelvic examination revealed a dimple-like cervix with no demonstrable opening, either visibly or by bimanual examination. Realizing that delivery of the dead fetus through the vagina was impossible, a cesarean section was recommended and accepted.

Upon opening the abdomen above the umbilicus, it was discovered that the intestines and omentum were so densely matted together and so firmly adherent to the entire body of the uterus, which revealed numerous fibroids varying in size from a walnut to the size of an orange, that it was with great difficulty, that a space large enough was found to make the uterine incision. The tubes and ovaries could not be demonstrated.

After removal of the macerated fetus, the placenta, which had thinned out, was noted to extend over the entire length of the posterior portion of the uterus, with absolutely *no line of cleavage demonstrable*. It appeared to have grown into the wall

The bio-assay of the tumor tissue was carried out after the tissue had been in fixation for some time, and no appreciable amounts of estrin were found. The extract of the fixative fluid in which the specimen was preserved proved too toxic for the animals.

She was re-admitted to the Beth Israel Hospital on Sept. 18, 1936, for the removal of a small lump under the nipple of the right breast which the patient noticed five days prior to admission. Physical examination revealed a firm elongated nodule about 2 cm. in diameter. This was not attached to the skin. The nipple was not retracted.

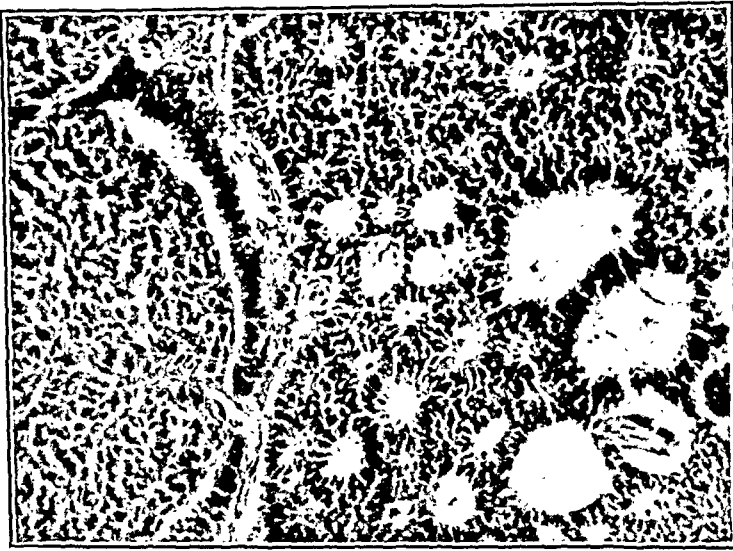


Fig. 1.—Granulosa cell tumor of the ovary showing radial arrangement of cells about a cavity resembling atypical follicles. In lower right hand corner is a more cellular area.

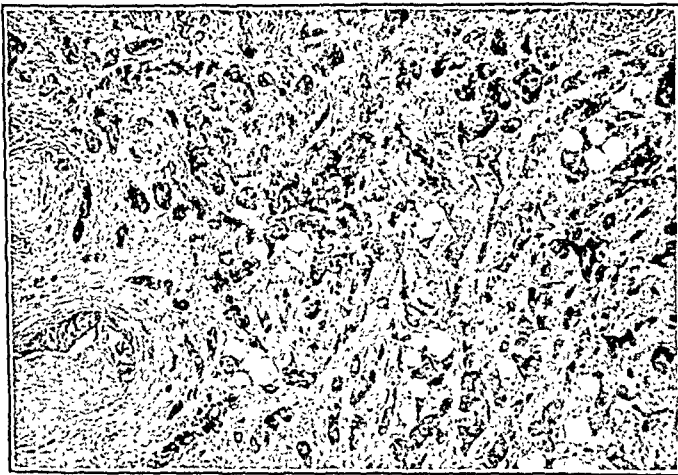


Fig. 2.—Scirrhus carcinoma of the breast.

She was operated upon on the following day. The lump was excised and the frozen section revealed a carcinoma. A radical mastectomy was then performed. A mass found in the axilla was also excised. The pathologic diagnosis was scirrhus carcinoma of the breast with lymph node metastasis (Fig. 2).

The patient made an uneventful recovery and was discharged Sept. 26, 1936. When last seen (May, 1937) no recurrence had been noted even though the patient absolutely refused to have postoperative radiation therapy.

In the light of the present knowledge of granulosa cell tumors of the ovary, and the questionable relationship between estrogenic and carcinogenic compounds,

PUERPERAL INFECTION FROM VINCENT'S ORGANISMS

FRANK W. PEYTON, A.B., M.D., LAFAYETTE, IND.

E. N., 19-year-old primigravida, was first seen Oct. 11, 1937. Family history was negative except diabetes mellitus. Past history revealed no acute infection, the patient was always in good health with the exception of an occasional sore throat. Later she stated that she had never had or received treatment for Vincent's or "trench mouth," or had she ever been in close contact with anyone known to have the disease. Menstrual history was negative, the last period being March 20, 1937. The pregnancy had gone along quite uneventfully. Examination showed a well-developed and well-nourished female estimated to be about thirty weeks pregnant. Throat was negative, teeth somewhat carious, thyroid not palpable, heart and lungs negative, blood pressure 116/70, pelvic measurements small, large varicose redundant flap of anterior hymenal ring, cervix soft, not eroded and showed no evidence of infection (smear not taken). Urinalysis and blood Wassermann were negative.

Pregnancy continued on normally until two weeks before delivery when an attack of coryza occurred, with elevation of blood pressure to 134/90 which subsided under treatment. Contractions started following spontaneous rupture of membranes, Dec. 26, 1937. After a total labor of six hours the patient was delivered by means of outlet forceps following central episiotomy of a normal, full term, living male infant. Local infiltration and pudendal block with $\frac{1}{2}$ per cent novocaine supplemented oral paraldehyde analgesia for the delivery and repair of episiotomy. Placenta and membranes were expressed intact by modified Credé. Estimated blood loss was 150 c.c. One hour later the uterus had relaxed to the extent where the cavity contained a clot of approximately 500 c.c. After expression of the clot there was fair tonicidity and patient bled, possibly, another 100 c.c. before complete cessation was brought about by oxytocics and massage.

The first six days of the post partum were uneventful, the highest temperature being 100° F. on the fourth day. Pulse ranged from 84 to 110. The lochia was moderate in amount, red in color the first four days, became scant and white on the sixth and seventh days. At no time was it foul. On the seventh day the patient experienced a chilly sensation following which temperature rose to 101° F. Examination revealed inflamed watery discharging nasal mucosa, extremely engorged breasts, chest clear, uterus 2 fingerbreadths above symphysis, firm and not tender. No tenderness over kidneys and the extremities were normal. Urinalysis was negative for albumin and cellular elements. The following morning (8th day) the temperature had risen to 103° F. Blood study showed 52 per cent hemoglobin, 3.2 million red blood cells and 16,000 white blood cells with 83 per cent being polymorphonuclears. The lochia suddenly became very profuse, fetid in odor, and varied during the day in appearance, from serosanguineous to greenish, thick mucopurulent containing an occasional minute clot of bright blood or a streak of blood. The patient had no complaints and was rapidly becoming more toxic, drowsy, and nauseated. The temperature was maintaining a rather constant level of 104° F. through the latter part of the day. Intravenous glucose, transfusion with 250 c.c. of citrated matched whole blood and sulphanilamide were administered. Early the ninth day a smear was taken of the lochia and under gentian violet staining the Vincent's organisms were discovered, there being 15 to 20 spirilla and 7 to 8 fusiform bacilli under oil immersion to the microscopic field. Innumerable *B. coli* and staphylococci were observed. Smears were negative for streptococcus, gonococcus, and *B. diphtheriac*. Blood culture and lochial culture were not done. At this time the patient was practically moribund. She was then receiving 2½ per cent glucose in normal saline by continuous phleboeclysis. Another transfusion of 300 c.c. was resorted to. The temperature had ranged from 103 to 104° F. throughout the day, and pulse 132-144. It was felt that therapy so far was to no avail. Four hours following the transfusion she was given 0.3 gm. of neosarsphenamine intravenously.

of the uterus and removal was impossible. Further exploration of the interior of the uterus revealed no demonstrable internal os, so with an assistant pressing his examining finger on the dimple-like cervix through the vagina, the operator cut down on the finger from the interior of the uterus in order to establish an opening for drainage. A gauze drain was placed in this opening, pulled through into the vagina, and the uterus closed in the routine manner, after the umbilical cord was amputated at the junction of the placental attachment. It was impossible to do a hysterectomy, because of the very dense adhesions of the intestines and omentum to the entire body of the uterus. A drain was inserted in the lower angle of the abdominal incision, patient was transfused, and was returned to her room with a bad prognosis.

The convalescence was stormy. After the third day, the drain in the uterus was removed through the vagina. There was little drainage from this source, but much from the drain in the abdomen.

Eighteen days postoperatively, she returned home in the ambulance, and during the first week at home, there was still no vaginal drainage but considerable drainage through the abdominal incision, which did not close until April, 1937 (nine months after the operation). During that period the patient was ambulatory.

In September, 1937 (fourteen months following the operation) she had a normal menstrual period, no period in October and a scanty period lasting approximately two weeks in November, 1937. Since then there have been no menstrual periods and her only complaint is an occasional hot flash.

In January, 1938 this patient was examined in our office. Vaginal examination revealed a nonmovable uterus about the size of a grapefruit and an external os of normal size, from which was exuding a small amount of clear watery discharge. The neck of the cervix was absent. The abdominal scar was firm, urine negative, bowels regular, blood pressure 150/70, weight 139 pounds. She claimed she never felt better in her life.

COMMENT

Our case demonstrates not only the successful outcome of leaving the placenta in the uterus, which in itself is unusual, in that it is the second successful case of this type to appear in the literature, but also demonstrates the point that placenta accreta is usually associated with other anatomical anomalies of the uterus.

As was previously stated, the external os appeared absent or so small as not to be visible, as was the internal os.

The presence of fibroids does not appear to be unusual in this type of case. The early prenatal distress this patient experienced can be explained by either the beginning degeneration of the fibroids, upon which the intestines and omentum became adherent with partial bowel obstruction, or the penetration of chorionic villi through the uterine wall into the omentum and intestines.

The former explanation of degeneration of the fibroids being the cause of the adhesions seems more likely because of what occurred during convalescence.

Undoubtedly the huge amounts of pus, which poured forth from the abdominal incision during the nine postoperative months, came from the continued degeneration of the large nodular fibroids.

This case is also unusual in that the patient was an elderly primipara with no abnormal menstrual history.

diagnosis of multiple pregnancy was made, one vertex and one breech presentation. The cervix was one and one-half fingers dilated, and x-ray film at this time verified our findings. At 12:15 P.M., on Nov. 13, 1936, the patient began to have uterine contractions. Fifteen hours later the cervix was fully dilated. Weak contractions were present. One and one-half hours later, three minims of pituitrin were given and repeated three times, so that in one and three-quarters hours she received a total of 12 minims of pituitrin with no effect on the uterine contractions. The septum in the vagina was severed and tied. After three and three-quarters hours in the second stage of labor, the first fetus, weighing 4 pounds, was delivered by low forceps. The second fetus, weighing 4.5 pounds, was extracted twenty minutes later after artificial rupture of the membranes. Fifteen minutes after the second delivery one placenta was expressed. An attempt at expressing the second placenta was made with no avail. Manual removal was attempted at this stage, after a loss of about 700 c.c. of blood. Up to this time the diagnosis had not been made and on inserting the hand into the uterus it did not seem to allow enough space to palpate the cavity of the uterus nor the placenta and, with the patient in incipient shock, a pulse of 160, it was decided to leave the placenta in situ and pack the uterus. Sixteen yards

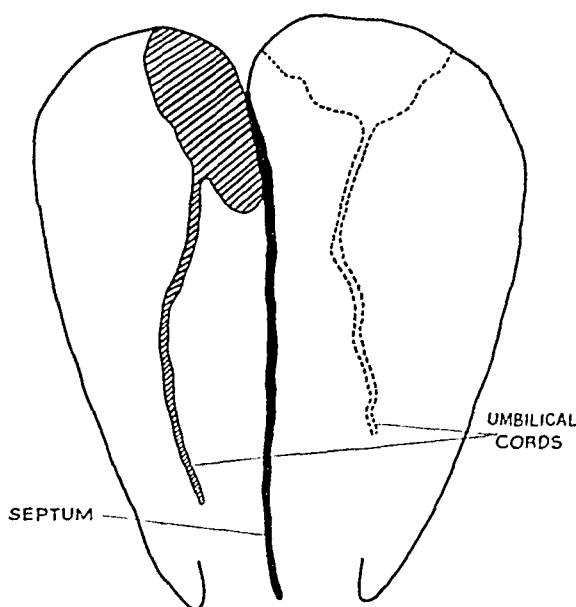


Fig. 1.

of iodoform gauze were inserted. Hypodermoclysis of 1,000 c.c. of saline with 5 per cent glucose was given. Shock treatment was instituted and the patient was put back to bed.

On the following day the patient had a chill for twenty minutes and a temperature of 104° F.; pulse 122; and respirations 24. Feeling that the placenta in the uterus was the source of the temperature and chill, it was decided again to attempt manual removal of the placenta. At this time the diagnosis of septate uterus was made. It was impossible to get a hand into the uterus to grasp the placenta which was attached high up in the fundal septal angle, where the septum and the fundus met. It was impossible to guide a placental forceps up to the body of the placenta and only very small pieces of it could be removed. The patient again went into incipient shock with a pulse of 170 to 190, and the uterus was again packed.

A transfusion of 500 c.c. of whole blood was given and appropriate shock treatment was again instituted. Hysterectomy was then decided upon. She was taken to the operating room and a supravaginal hysterectomy done, following which she again received a 500 c.c. transfusion. Pathologic specimen revealed a septate uterus with a retained placenta in the right horn which separated easily. The patient developed a wound infection but recovered fully.

Six hours after the neoarsphenamine was administered the temperature and pulse slowly fell and in eighteen hours were 100° F. and 116, respectively. The patient was then cheerful, alert, and asked for food. The lochia had lessened considerably but was still foul, and smear showed an occasional fusiform bacillus but no spirilla. Latter part of the tenth day temperature started up again and in twelve hours reached 103° F., pulse 124. Slight pain in pelvis began for first time, along with tiredness and depression. The temperature remained elevated and the following day (eleventh) a pelvic examination was done. The episiotomy wound was well healed, vaginal walls normal, cervix well involuted, stellate lacerations of os, and canal filled with a mucopurulent discharge. About the portio vaginalis there were three irregular reddened patches covered by a pseudomembrane. Smears were taken from the patches and cervical canal. Moderate tenderness was present in both adnexal regions upon gentle bimanual examination, but no masses were made out. No filling in of cul-de-sac. Again Vincent's organisms were found on the smears. Because of the recurrence of positive smears and fever, another 0.3 gm. of neoarsphenamine was administered. Temperature and pulse fell to normal levels in eight hours and the pelvic pain and tenderness disappeared. Except for unexplained single reading on the fourteenth day of fever to 101° F., the temperature continued normal until patient was released from the hospital on twentieth post-partum day. Patient appeared to be in good health when released, hemoglobin 68 per cent, pelvis normal, cervical patches had disappeared, and smear showed only an occasional staphylococcus.

The etiology of this infection can easily be accounted for by an endogenous or exogenous route. From 16 possible sources or contacts, the patient, her husband, three nurses (one in charge of perineal care) and an aid in the kitchen, all revealed definite fusiform bacilli and spirilla in smears from gums. It was also disclosed that three weeks previously a maternity patient on the same ward was suffering from Vincent's angina, but her infection was confined to oral cavity.

723 LAFAYETTE LIFE BUILDING

MULTIPLE PREGNANCY IN A SEPTATE UTERUS WITH RETAINED ADHERENT PLACENTA

ELIAS RAUCH, M.D., NEW YORK, N. Y.

(From the Service of the Jewish Maternity and Beth Israel Hospitals)

THE literature, while mentioning the possibility of the occurrence of multiple pregnancy in a septate uterus, discloses only a limited number of such cases. These pregnancies usually terminate in abortion for either one or both fetuses.

Vastal, in 1700, described a case of double uterus. Lane, in 1885, reported a case of double uterus with a fetus in each body terminating in abortion. DePage described a uterus with three cavities. Double uterus with a single pregnancy has been reported numerous times. Kats, in 1896, described two cases of abortion in bicornate uteri. Pfannenstiel, in 1892, collected 18 cases of full-term pregnancies in two uteri. Jellinghaus also reported a case of multiple pregnancy in a double uterus with abortion. Houlton, in 1925, reported a case of multiple pregnancy in a uterus bicornis bicollis.

C. W., aged 25, para 0, gravida i, was admitted to the Prenatal Clinic of the Jewish Maternity Hospital in the seventh month of pregnancy. She had already gained 51 pounds during her pregnancy. The prenatal, past, and family history were essentially negative. Vaginal examination at this time disclosed a septate vagina.

On November 12, in the thirty-sixth week of pregnancy, she was admitted to the Jewish Maternity Hospital with a history of ruptured membranes, but not in labor. There was some pitting edema of both ankles. Blood pressure was normal. A

pain and weakness. A review of the other general systems revealed no other abnormalities. Physical examination disclosed a patient who was in shock and markedly anemic. The entire lower abdomen was tender. A diagnosis of ruptured ectopic pregnancy was made. At operation a ruptured left tubal pregnancy was found. The tube and its contents were removed. The peritoneal cavity was cleared of a large amount of fresh blood. The uterus was twice the normal size. This organ was incised and a fetus and placenta were found close to the left cornu. These were removed. The patient's postoperative course was relatively mild. Transfusion and venoclysis were resorted to and she left the hospital on Oct. 26, 1937, eighteen days after her admission.

Pathologic Report.—Specimen consisted of a tube 10 cm. in length, the proximal portion of which was dilated, dark red in color and measuring 5 cm. in diameter. In the hemorrhagic area of the tube was an opening communicating with the lumen. In the lumen was a fetus, 1.8 cm. in length, which was completely enveloped by its membranes. Accompanying the tube was the fetus removed from the uterus which measured 3.7 cm. in length, and its placenta.

COMMENT

The above case is of special interest because of the difference in size of the two fetuses. The question of superfetation naturally arises in all twin pregnancies. Since the fetus from the tube was so much smaller than its mate from the uterus, one could assume that the smaller one was the younger. On the other hand, the tube being an heterotopic site, it might not have predisposed to the normal rate of growth and hence the smaller size.

Murray, Edmundo G.: *Changes in the Cells of the Vagina*, Arch. f. Gynäk. 165: 635, 1938.

The author describes a simplified method of cell counts in vaginal strippings. From his studies on 128 women he concludes that the vaginal mucosa undergoes two definite cycles, a "folliculin phase" and a "lutein phase." During the folliculin phase, the vaginal mucosa undergoes marked regeneration especially in the superficial layers. During the lutein phase marked proliferation of the stratum germinativum and the stratum spinosum takes place.

The vaginal mucosa remains in the lutein phase throughout pregnancy, and the author was unable to find any evidence of cyclic changes. Acute inflammatory conditions of the mucosa result in marked inhibition of these cyclic changes. Genital hypoplasia and primary amenorrhea produce a definite atrophy which can be overcome by the administration of estrogenic substances. By contrast, secondary amenorrhea and irregularities of menstruation result in excessive cyclic changes in the vaginal mucosa. These changes can also be brought back to normal by the use of estrogenic hormones.

The senile vagina shows less differentiation than does the menopausal vagina. Four types of atrophy are described in detail, the author believing that this type of fine differentiation is helpful in arriving at a true definition of the functional and clinical status of the genitalia.

RALPH A. REIS.

PATHOLOGIC REPORT

Gross.—Somewhat asymmetrical appearing uterus with arcuation, total length 14 cm., transverse diameter 14 cm., indentation 8 mm.; the left side has a thickness of 5.5 cm., the right 6.75 cm. The cut edge had an ovoid opening, with a transverse diameter of 7 cm. and an anteroposterior diameter (in its present condition) of 2.5 cm. There was a sagittal septum which measured about 3 mm. in thickness; after stretching the septum it measured 5.5 cm. The serosa appeared normal except for some distended veins and a few small, firm, slightly protruding, grayish-white spots (small myomas?). The ligaments were cut short. In the upper portion the specimen was rather soft with little difference in consistency between the both sides. The lower portion was moderately firm.

On the left side the inside of the uterine cavity was diffusely light brownish red with numbers of small, soft coagula, partly lying loose on the surface, partly adherent. Numbers of distended thrombosed veins were seen in the wall, notably in the middle of the fundus.

On the right side a placenta was inserted, occupying the upper half of the specimen. Otherwise the surface looked as described from the other side. The placenta separated easily. The cut edge on this side did not show thrombosed veins, but some very wide empty ones. A flat fairly soft, inelastic piece 5 by 2.5 cm., purplish-gray, without distinct markings showed on microscopic section a probable decidual origin.

COMMENT

This case either was one of superfetation, with the fertilization of the two ova in the same or different menstrual cycles, or simultaneous impregnation of two ova, one from each ovary, with nidation of each in a separate compartment of the septate uterus; each fertilized ovum having its own corpus luteum. Because of the half pound difference in size of the fetuses, the first supposition, superfetation, is probably the correct one.

515 PARK AVENUE

COMBINED INTRA- AND EXTRAUTERINE PREGNANCY

M. EDWARD MARTEN, M.D., AND LEO M. MEYER, M.D., BROOKLYN, N. Y.

(From the Department of Pathology, Samaritan Hospital)

COMBINED uterine and tubal pregnancies have been recorded relatively frequently (7 cases in the first half of the year 1937). Frank, in his textbook, states that extra- and intrauterine pregnancies occurred once in 105 ectopics. Teacher makes only casual mention of the subject in his book. In 1913 Neugebauer collected 243 cases of combined pregnancies. Novak reviewed the literature from 1913 to 1926 and added 32 more cases, and discussed fully the incidence, clinical characteristics, diagnosis and treatment of this unusual condition. Hefferman and Faxon, in 1935, summarized the literature up to that year and found a total of 282 cases.

CASE REPORT

Mrs. C. I., white, age 26 years, para i; gravida iii, was admitted to the Gynecological Service on Oct. 8, 1937, complaining of cramp-like pains in the lower abdomen of one week's duration. These abdominal pains were associated with vomiting, dizziness and weakness. Her past history indicated a spontaneous full-term delivery three years prior to the present illness. Subsequent to this the patient had a miscarriage followed by a curettage five months prior to her admission to the hospital. The patient last menstruated on Aug. 12, 1937. Up until this date her periods had been regular every twenty-eight days lasting two to four days. No history of vaginal bleeding was associated with the present attack of abdominal

Seven women in whom prolan determinations revealed a positive or increased amount of prolan in the urine were skin tested. Five of these showed no reaction. Two showed a wheal and erythema indicative of a nonpregnancy. These findings show that as a test for prolan in the body the intradermal injection of pituitary-like substance is of no value. In 15 nonpregnant women who showed positive pregnancy skin readings only 5 had positive prolans, whereas 2 women with a positive urinary prolan gave a negative pregnancy skin reading.

In the third part of this study, 33 men were tested.

These included physicians, laboratory technicians and workers and patients on the wards of the hospital. Of these 33 men, 8 gave a nonpregnancy reading; 25 gave a positive pregnancy reading. Six of the men who gave positive pregnancy readings were further studied for their prolan content. Five of these prolan studies were negative, indicating no increase in their prolan excretion in the urine. One man, 55 years of age, showed a positive prolan.

TABLE III. SUMMARY OF SKIN TESTS IN PREGNANT WOMEN, NONPREGNANT WOMEN AND IN MEN

		NO. OF PREGNANCY REACTIONS	NO. OF NONPREGNANCY REACTIONS
Number of pregnant women	88	80	8
Number of nonpregnant women	40	27	13
Number of men	33	25	8
Total number of cases studied	161		

SUMMARY

1. The intradermal administration of anterior pituitary-like substance of pregnancy urine as a diagnostic test for pregnancy shows the following deviations from expected results on proved cases:

a. Of expected positive results in 88 pregnant women there were 8 who gave negative results.

b. Of expected negative results in 40 nonpregnant women, only 13 gave a negative pregnancy reading, 27 were positive for pregnancy.

c. Of expected negative results in 33 men, 8 showed the expected result, 25 showed positive pregnancy tests.

2. Prolan studies done on 10 nonpregnant women who gave a definitely positive pregnancy reading were negative.

3. Prolan studies done on six men who gave a definitely positive pregnancy reading were negative in 5 and positive in 1.

4. Of 7 nonpregnant women with a positive prolan, 5 gave a positive pregnancy test and 2 a negative test.

5. The results are in substantial agreement with other recent critical analyses of this diagnostic procedure.

The authors wish to thank Dr. D. A. McAteer, Director of the Surgical Service, and Dr. H. B. Matthews, Director of the Obstetrical Service, for their cooperation.

The authors also wish to thank Dr. Charles H. Birnberg for his kind suggestions during this study.

The Anterior-Pituitary-like substance used was antuitrin-S (Parke-Davis & Co.).

MODIFICATION OF HILLIS-DELEE OBSTETRIC STETHOSCOPE

RICHARD TORPIN, M.D., AUGUSTA, GA.

*(From the Department of Obstetrics and Gynecology, University of Georgia
School of Medicine)*

THIS modification consists of a head band with a four or five inch projecting rod with the distal end bifurcated and assembled with a thumb screw to form a clamp for the bell portion of any stethoscope as illustrated in Figs. 1 and 2. Its value has been demonstrated by six years' use in clinic and private practice. The chief advantage lies in the ability of the obstetrician to use a stethoscope to which he is accustomed.

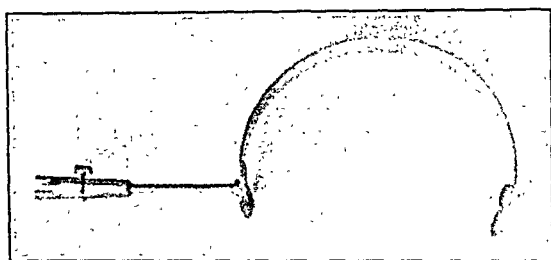


Fig. 1.

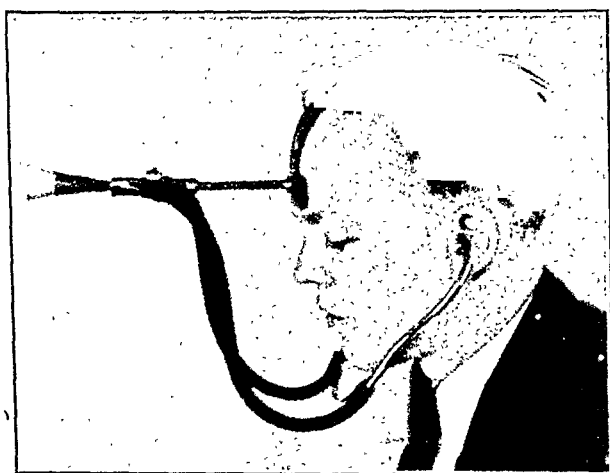


Fig. 2.

Since its introduction twenty years ago the Hillis-DeLee head stethoscope has become an essential part of the equipment of almost all modern hospital delivery rooms. However it is of great value in the prenatal examination of patients in the clinic or in the individual physician's office where it is often lacking because of the expense. This modification which does not require the additional cost of an attached stethoscope is far less expensive to manufacture and should sell for not more than a third of the cost of the original model.

Correspondence

Dear Editor:

The practice of medicine in our "poor white" mountain districts of the South is a baffling proposition and one which I feel our best social-medical minds should be working on.

The grub farmer living far up on a creek or the miner living in an abandoned mining camp has two choices in time of sickness. He may hire a car and go twenty-five miles to either a town physician, the county health doctor, or the mining camp physician; or he may send for a doctor for a fee which may mean the sale of his cow or hog which is part of his next year's food supply.

No one is to blame for this condition. Most creek calls involve a half day in time and extreme wear and tear on the car, which makes a high fee necessary. As a result of this, the mountain people are in the habit of employing all sorts of weird home remedies, granny midwives, local "cancer doctors," and faith healers. As is to be expected there is no prenatal care with the resulting high maternal and infant mortality. Ordinary child hygiene is practically unknown.

The population is increasing at such a rate that suddenly we are going to awake to the fact that we have a large group of people physically and mentally unable to cope with our present civilization.

Should not the medical profession as a whole express some interest in this situation which is not only a future menace, but a dark blot on our medical conscience?

ELEANOR HAMILTON, M.D.

Myra, Kentucky,
August 5, 1938.

NOTE: This communication comes from a little mining town in the mountains of eastern Kentucky, which is well termed a "Medical Missionary Outpost." It is written by a well-trained young physician who is duly appreciative of the difficulties which beset these people in obtaining adequate care in pregnancy. How shall this problem be solved? Is it to be by the systems of relief so widely disseminated at the present time, with their doubtful effect on mind and body, or shall it be by some system of adequate medical service developed and supervised by the profession itself? It seems necessary to build up a broader and a different program, for the social, economic-medical question is confusing, and it is difficult to speak with clearness until sufficient familiarity has been gained by constant association with the problem. The doctor, with a public health and sociologic point of view, should be able to supply the necessary guidance. But what can he do without funds, either of the individual or the community, and how shall these be employed?

The Federal Children's Bureau is endeavoring to supply an answer. Let us hope it can be done successfully without an overpowering bureaucracy, which is frequently debilitating rather than helpful. There must be a way to answer Dr. Hamilton's questions and those of others like her, in similar, often thankless, positions.

EDITOR.

Society Transactions

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF APRIL 15, 1938

The following papers were presented:

Two Cases of Intersexuality. Dr. William J. Carlisle and Dr. C. J. Geiger. (For original article, see page 1047.)

Technic and Results of Routine Fetal Electrocardiography During Pregnancy. Dr. Erwin O. Strassmann. (For original article, see page 986.)

A Case of Acephalus Holoacardius. Drs. Henry Buxbaum and David V. Wachsman. (For original article, see page 1055.)

The Experimental Production of Intersexuality in the Female Rat. Drs. R. R. Greene, M. W. Burrill, and A. S. Ivy. (For original article, see page 1038.)

Liver Presentation. Dr. Edward Allen. (For original article, see page 1060.)

Sarcoma of the Uterus. Dr. W. C. Danforth. (For original article, see page 1062.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF APRIL 1, 1938

The following papers and discussions were presented:

Dysmenorrhea. Drs. Lawrence Kurzrok, C. Burnberg and S. Livingston.

A Comparative Study of the Classical and Cervical Cesarean Sections at the Brooklyn Hospital in a Series of 164 Cases. Dr. John Casagrande. (For original article, see page 1033.)

Supravaginal Hysterectomy. Dr. W. T. Dannreuther.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Ovarian Pathology

Béclère, C.: Etiology and Pathogenesis of Uterine Hemorrhage of Ovarian Origin, *Bull. Soc. d. obst. et de gynec.* 26: 759, 1937.

Béclère has had occasion to study 158 cases of functional hemorrhage of ovarian origin in a total of 280 hysterosalpingographies performed in women with hemorrhage of unknown origin.

Uterine hemorrhage of ovarian origin may be divided into 2 groups. In the first there is a tumor of the ovary either liquid or solid. These cases are uncommon. In most cases the ovary is normal in size and the hemorrhages occur during active sex life. The author divides the latter group into three classes, namely, hemorrhages due to congenital lesions of the ovary (15 cases), hemorrhages due to infection of the ovary (93 cases), and hemorrhages due to premenopausal ovarian disturbances (50 cases).

Clinically there may be increased menstrual flow, irregular bleeding, and periods of amenorrhea alternating with hemorrhage. Histologically there is found benign glandular hyperplasia. The author believes that it is by means of hystero-graphy that we can best separate the cases of functional bleeding from those associated with lesions. The uterine image may be normal but usually there is a jagged uterine picture first described by the author. One observes a series of small contiguous projections in a normal-sized uterine cavity.

In the cases of uterine bleeding due to congenital disturbances, a cure may be brought about by the use of corpus luteum hormone. In the cases due to infection, diathermy and anti-infection vaccines produce quick relief. For the premenopausal group, roentgen ray therapy is the treatment of choice.

J. P. GREENHILL.

Opocher, E.: The Sclerotic Degenerative Changes of the Ovary, *Folia Demograph.-Gynaec.* 34: 523, 1937.

Studying 927 cases in which sclerotic changes in the ovary were found at operation, the author concludes that the clinical expression of these changes is manifested in three principal symptoms: Pain, menorrhagia or metrorrhagia, and sterility. The diagnosis is always difficult, if not almost impossible, especially when there exist other symptoms referable to the genital organs.

Therapy must of necessity be varied according to the particular condition in each case, but the author feels that in aggravated cases the treatment usually is surgical, consisting in resection of the ovary. This procedure has given the author good results, both primary and remote.

MARIO A. CASTALLO.

Cooke, W. R.: Cystic and Solid Tumors of the Ovary, *Texas State J. Med.* 32: 759, 1937.

Studying the ovarian tumors seen in the laboratory of the University of Texas from 1927 to 1935, the author arrives at the following conclusions: (1) Most ovarian cystic masses are harmless, undergo spontaneous resolution and rarely require operation except on account of development of such accidents as hemorrhage,

torsion, or infection. (2) The relatively few ovarian cysts which require operative removal for cure rarely become a menace to the life of the patient until they have attained a size or an age beyond the ordinary limits of the harmless types of cyst. (3) Hence, in the case of small cysts, operation should be deferred (under frequent observations) until a reasonable certainty exists that the cyst is of the type which will require operative removal for cure.

J. P. GREENHILL.

Bufe, W.: Frequency of Cysts of the Ovary as an Accidental Finding During Autopsies, *Zentralbl. f. Gynäk.* 61: 632, 1937.

In a series of 100 pairs of ovaries removed at autopsies, Bufo found cysts present in 77 per cent. The types of cysts encountered were: small cystic degeneration, 22 per cent; follicle cysts, 55 per cent; corpus luteum cysts, 9 per cent; hilus cysts, 7 per cent; and parovarian cysts, 2 per cent.

J. P. GREENHILL.

Varangot, J.: A Tumor of the Theca Interna of the Ovary, *Bull. soc. d' obst. et de gynec.* 26: 699, 1937.

During the last few years a special group of tumors have been isolated from ovarian neoplasms which manifest endocrine activity and secrete the estrogenic hormone. In this special group which may be called feminizing tumors, there are two anatomic varieties, one of which arises in the granulosa and the other in the theca interna. Varangot reports a case of the latter variety. The tumor consisted of a fibroma of the ovary which contained large quantities of intracellular cholesterides. Thus far 23 cases of this kind have been reported, the first ones having been described by Loeffler and Priesel. Varangot saw another case in Montreal.

J. P. GREENHILL.

Mocquot, Moricard, Palmer, and Gothié: A Case of Thecal Tumor, *Bull. Soc. d' obst. et de gynec.* 26: 703, 1937.

The authors report a thecal tumor of the ovary in which the manifestations of estrogenic activity were particularly intense.

J. P. GREENHILL.

Patterson and McCullagh: A Case of Theca-Cell Tumor of the Ovary in a Woman Aged 92 Years, *J. Obst. & Gynaec. Brit. Emp.* 43: 1186, 1936.

This case is recorded as an example of a rare ovarian tumor occurring in extreme old age. It appears to be the oldest recorded case by a wide margin. The growth proved to be of the theca-celled type of granulosa-cell tumors.

The patient, aged 92 years, was admitted in December, 1935, for backache and vaginal bleeding due to an abdominal tumor the size of a large grapefruit, which felt like a pedunculated fibroid.

The menopause occurred thirty-six years before, but four years ago slight irregular vaginal losses of blood had begun, and these lately became continuous, worse at intervals.

Subtotal hysterectomy was performed and both tubes and ovaries were removed.

The endometrium showed estrogenic hypertrophy with cystic dilatation of the glands, and resembled the normal premenstrual endometrium of a young woman, but the hypertrophy was more marked.

J. P. GREENHILL.

Harms: Granulosa Cell Tumors in Young Girls, *Zentralbl. f. Gynäk.* 61: 17, 1937.

The author describes two granulosa cell tumors seen in girls 8 and 14 years old, respectively. The eight-year-old girl developed a precocious puberty. In both cases estrogenic hormones were demonstrated in the tumor implants. In the child with

precocious puberty there was an unexplained positive Aschheim-Zondek reaction present. These cases illustrate that uterine hemorrhages in young girls should arouse a suspicion of granulosa cell tumor.

J. P. GREENHILL.

Rhoads, J. E., and Terrell, Alexander W.: Ovarian Fibroma With Ascites and Hydrothorax (Meig's Syndrome), J. A. M. A. 109: 1684, 1937.

The knowledge that this association of pleural effusion with a benign fibromatous tumor of the pelvis exists is extremely important from the standpoint both of prognosis and of treatment, since most pelvic tumors causing pleural effusion are malignant and the effusion is the result of pleural or pulmonary metastases. A series of seven cases presenting the syndrome of fluid in the chest in association with ovarian fibroma were recently reported by Meigs and Cass. The authors report another case in which the tumor weighed 810 gm. and in which the amount of fluid in the chest exceeded the amount of ascitic fluid. No satisfactory explanation of the associated hydrothorax has as yet been offered.

GROVER LIESE.

Glasunow, M.: The Histology and Histogenesis of So-called Ciliated Epithelial (Serosus) Cysts of the Ovary, Arch. f. Gynäk. 164: 358, 1937.

The author studied 15 cases of so-called ciliated epithelial tumors (cysts) of the ovary and concludes that this type of epithelium is identical with that of the uterine tubal mucosa rather than resembling that of the ovarian tunica as was formerly held. Such cysts arise from postnatal implantation of Müllerian epithelium although some may arise from embryonic rests of Müllerian ducts. These cysts should, therefore, be called either tubal epithelial cysts or Müllerian cysts. This epithelium produces mucus but only in small quantities. The term pseudomucinous is an all inclusive one including both the type of cyst under consideration and others of different histogenesis. Müllerian duct epithelium can and does produce ciliated epithelial cysts as well as pseudomucinous cysts.

RALPH A. REIS.

Pund and Gotcher: Granuloma Venereum of Uterus, Tubes, and Ovaries, Surgery 3: 34, 1938.

The patient, a 28-year-old negress, on admission complained of vaginal hemorrhages for last two months. She had a palpable mass in left lower abdominal quadrant, noticed first five months ago and gradually enlarging. Further examination showed a large, red, easily bleeding cervix and a hard mass, filling pelvis and reaching up almost to navel. Wu and Kahn reactions negative. Under conservative observation, with preliminary diagnosis of chronic inflammatory process, temperature fluctuated between 100° and 104° F. After two months the genitalia were removed. Operation was very difficult and patient died next day. Necropsy refused.

Microscopic study of removed organs established a heretofore undescribed entity, namely involvement of uterus, tubes, and ovaries by a granuloma inguinale. Apparently this infection can ascend following delivery. In a previous paper (J. A. M. A. 108: 1401, 1937) these same writers had discussed in detail a case of granuloma venereum of the cervix uteri closely simulating carcinoma.

HUGO EHRENFEST.

Books Received

PRACTICAL CLINICAL GYNECOLOGY. By Henry C. Falk, M.D., Clinical Professor of Gynecology, New York University College of Medicine, etc. Illustrated, 393 pages. American Journal of Surgery, New York, 1938.

A CHALLENGE TO SEX CENSORS. By Theodore Schroeder. Privately printed. New York City, 1938.

ENDOGENE ENDOKRINOTHERAPIE IN DER GYNAEKOLOGIE. Aetiologie und Behandlung des Karzinoms. Von Dr. Jules Samuels, Chirurg und Frauenarzt in Amsterdam, etc. 182 Seiten. A. W. Sijthoff's Uitgeversmaatschappij, N. V. Leiden-Holland, 1938.

BLUTUNG UND FLUOR. Von Professor Dr. Hans Runge, Universitaets-Frauenklinik, Heidelberg. Dritte verbesserte Auflage, mit 17 Abbildungen. Theodor Steinkopff, Dresden, 1938.

SEXUAL HORMONE. Von R. Oppenauer and F. Dessau. 121 Seiten. Uitgeverij Dr. W. Junk, Den Haag, 1938.

THE PITUITARY GLAND. An investigation of the most recent advances. Proceedings of the Association for Research in Mental and Nervous Diseases, December 28 and 29, 1936. Williams & Wilkins Company, Baltimore, 1938.

MATERNAL CARE, Complications. Prepared under editorship of Dr. Fred L. Adair, and approved by the American Committee on Maternal Welfare, Inc. University of Chicago Press, 1938.

CLINICAL ROENTGENOLOGY OF THE DIGESTIVE TRACT. By Maurice Feldman, M.D., Assistant Professor of Gastroenterology, University of Maryland, etc. With 357 illustrations in the text, 1014 pages. William Wood & Co., Baltimore, 1938.

GINECOLOGIA OPERATORIA. Indicaciones y tecnica. Par Eduardo A. Fox and Jose A. Ibarra, Servicio del Hospital Rivadavia, Buenos Aires. Ancieto Lopez, editor, Buenos Aires, 1936.

TEXTBOOK OF GYNECOLOGY. By Arthur Hale Curtis, M.D., Professor and Chairman of the Department of Obstetrics and Gynecology, Northwestern University Medical School, etc. Third edition, reset; 603 pages with 318 illustrations. W. B. Saunders Company, Philadelphia, 1938.

A B C OF THE VITAMINS. By Survey in Charts. By Jennie Gregory, M.S. Foreword by Walter H. Eddy, Professor of Physiologic Chemistry, Teachers College, Columbia University. Williams & Wilkins Company, Baltimore, 1938.

DISEASES OF WOMEN. By Ten Teachers, under the direction of Clifford White. Edited by Sir Comyns Berkeley, Clifford White and Frank Cook. Illustrated, 492 pages. Sixth edition. William Wood and Company, Baltimore, 1938.

THE MAN TAKES A WIFE. A Study of Man's Problems in and through Marriage. By Ira S. Wile, M.D. 277 pages. Greenberg, Publishers, Inc., New York, 1937.

ADVENTURES IN RESPIRATION. Modes of Asphyxiation and Methods of Resuscitation. By Yandell Henderson. Illustrated, 316 pages. Williams & Wilkins Company, Baltimore, 1938.

GRUNDLAGEN DER GYNAEKOLOGISCHEN KURZWELLEN-THERAPIE. Von Dr. med. Ernst Raab, Berlin. Mit 29 Abbildungen, 66 Seiten. Ferdinand Enke Verlag, Stuttgart, 1938.

INNERE MEDIZIN IN DER CHIRURGIE. Von Dozent Dr. H. Frh. v. Kress, und Dr. W. Kittler, chirurgische Universitaets-Klinik in Muenchen. 144 Seiten. Ferdinand Enke Verlag, Stuttgart, 1938.

BIOGRAPHY OF THE UNBORN. By Margaret Shea Gilbert. Illustrated, 132 pages. The Williams & Wilkins Company, Baltimore, 1938.

PRINCIPLES AND PRACTICE OF MEDICINE. Originally written by the late Sir William Osler. Thirteenth edition, revised by Henry A. Christian, Hersey professor of the theory and practice of physis, Harvard University; physician in chief, Peter Bent Bingham Hospital, Boston. 1424 pages. D. Appleton-Century Company, Inc., New York, 1938.

NURSING, an Art and a Science. By Margaret A. Tracy, R.N., A.B., M.S., director, Training School for Nurses, University of California, San Francisco, and Collaborators. 559 pages with 183 illustrations. C. V. Mosby Company, St. Louis, 1938.

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. Newman Dorland, A.M., M.D., F.A.C.S. Eighteenth edition, revised and enlarged, with 942 illustrations, including 283 portraits, 1607 pages. With the collaboration of E. C. Miller, M.D., College of Virginia. W. B. Saunders Company, Philadelphia, 1938.

Item

American Board of Obstetrics and Gynecology

The general oral, clinical and pathological examinations for all candidates, Part II Examinations (Groups A and B), will be conducted by the entire Board, meeting in St. Louis, Missouri, on May 15 and 16, 1939, immediately prior to the annual meeting of the American Medical Association. Notice of time and place of these examinations will be forwarded to all candidates well in advance of the examination dates.

Application for admission to Group A, May, 1939, examinations must be on file in the Secretary's Office by March 15, 1939.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Dr. Floyd E. Keene, of Philadelphia, a member of the Editorial Board of the JOURNAL and a frequent contributor to its pages, died at his home in Wynnewood, Pa., on November 15, 1938. An appropriate obituary will be published in a forthcoming issue.

In the article by Dieckmann and Brown "Hypertension and Pregnancy" in the November issue, page 811, the table heading should read "B.M. (44575) Pre-eclampsia" instead of "Basal Metabolism," B.M., representing the patient's name.

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UTERINE BLEEDING WITH VIRILISM*

VIRGINIA G. RHEUBY, M.D., WILMINGTON, DEL.

(From the Gynecological and Pathological Services of the Woman's Hospital of Philadelphia)

THIS patient, a 21-year-old, colored, single female, illustrates an unusual type of uterine bleeding. She began to flow at thirteen and had a normal menstrual cycle thereafter. During her eighteenth year she noticed an incipient growth of hair on her chin, cheeks, and upper lip. Soon her menstrual periods became increasingly more abundant, and the interval between the bleeding grew shorter. She was chronically tired, had vertigo, anorexia, and her psychic condition was far from serene with the consciousness of her unfeminine appearance. She gave up her job and, aside from her visits to several physicians, remained secluded. By the autumn of 1936 the hypertrichosis required shaving every other day, and the bleeding was severe, occasionally lasting as long as a month, with irregular short intervals.

Various physicians consulted seemed to have presumed that she had committed an abortion, and she was apparently treated on that hypothesis, or on the basis of a mild pelvic inflammation. In October, 1936, she had a transfusion. When she was admitted to the Gynecological Service of the Woman's Hospital of Philadelphia, Jan. 4, 1937, the patient was not acutely ill, although she had bled most of the month previously. Her hemoglobin was 52 per cent Dare, R. B. C. 2,610,000, W. B. C. 15,000, polymorphonuclear leucocytes 78 per cent, lymphocytes 22 per cent, blood sedimentation time 155 minutes, temperature 98.4°, pulse 96, and respiration 20.

A physical examination revealed no deviation from the normal, except a slightly low blood pressure, hypertrichosis, and pallor. Her voice was contralto. The pelvic examination disclosed no signs of inflammation. The clitoris protruded sufficiently to separate the labia majora and measured 3.75 cm. long by 0.75 cm. diameter. Aside from size it was not abnormal. The vaginal introitus was intact. The cervical os easily admitted a cotton applicator, and the cervix was soft, pink, intact, and mobile. The fundus was slightly enlarged, soft, smooth, mobile, anterior, and tender. In the right and left fornices were two discrete, firm, ovoid masses about 5 by 3 by 2 cm. in size.

The following day a diagnostic curettage of the uterus was performed. The uterine cavity measured 7.5 cm. and abundant, thick, soft, irregular scrapings were secured.

Dr. Berta Meine, Pathologist, examined the scrapings and believing that the diagnosis lay between severe hyperplasia of the endometrium and adenocarcinoma, and feeling the situation too precarious to risk a final diagnosis, returned the pathologic report as adenocarcinoma.

The patient was given a blood transfusion and on Jan. 13, 1937, Dr. Fetterman performed a panhysterectomy with a bilateral salpingo-oophorectomy. No radiation was given. The patient made a rapid uneventful convalescence, and has been well since. There has been no diminution of the hypertrichosis and size of clitoris. Basal metabolic rate tests have not fluctuated more than four points from plus 16.

*Read at a meeting of the Obstetrical Society of Philadelphia, October 7, 1937.

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X-rays of the skull have demonstrated an apparently normal sella turcica with no evidence of pituitary abnormality. Roentgen studies made prior to the second operation to discover any metastases failed to disclose any evidence of osteoporosis and an intravenous urogram presented a picture of a normal urinary tract, without any displacement of the kidneys by suprarenal glands. The patient refused air injections in the renal region designed to indicate the presence of an adrenal neoplasm. At no time have hormone assays been made owing to lack of resources and later the reluctance of the patient.

The photograph (Fig. 1) of the specimen was taken within one hour of operation and shows the normalized uterus and tubes, and the enlarged microcystic ovaries. On section of both ovaries, we discovered an area above each hilum that was grayish orange, slightly softer than the remainder of the tissue. Aside from these yellowish places, the ovaries did not differ greatly from the firm, thick tunica microcystic ovaries we have found so frequently accompanying hyperplasia of the estrin type.

Careful microscopic sections through each entire ovary appeared almost identical (Figs. 2 and 3). The ovaries showed follicles in all stages of normal development

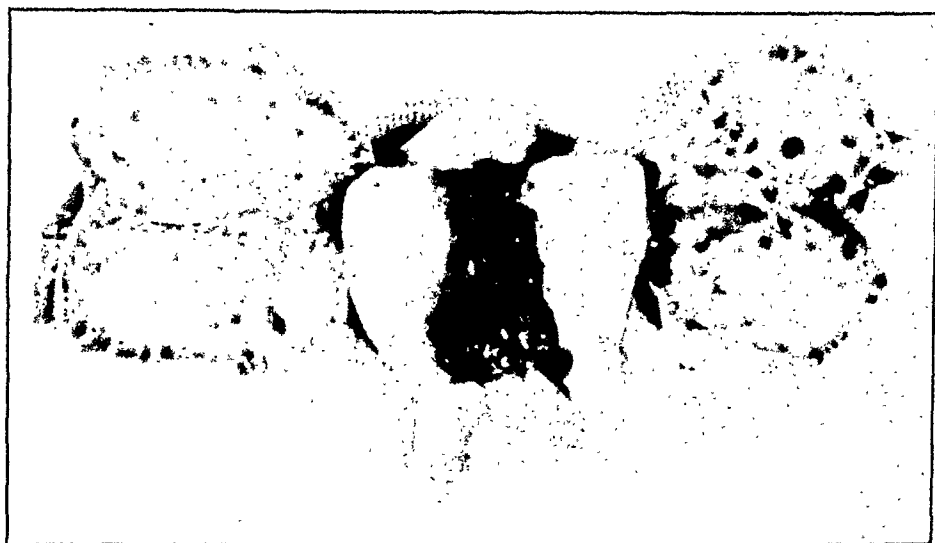


Fig. 1.—Photograph taken by M. Cousens of uterus, tubes, and ovaries immediately after operation.

and the periphery of each ovary was set with multiple small follicular retention cysts covered by a thick fibrous tunica. There was but one corpus album and no corpora lutea. In the areas of the yellow-gray substance there were definite structures unusual to ovaries. Surrounded by a fairly thick mass of cells (that closely resembled theca lutein cells) was an area about the size of a Graafian follicle in middevelopment, in which there were wisps of connective tissue and what might have been small fat cells. This core of tissue faintly suggested the texture of a fibroma ovarii. But it was very different from the fibroma ovarii, for there the thin spidery tissue was diffuse, while in these ovaries the thin bits of tissue formed the core of a definite structure pattern, repeated often in either ovary. Occasionally one saw a thin walled blood vessel in the core, but no sign of hemorrhage. These structures appeared only in the area where grossly the yellow tissue was apparent. In no way did they suggest adrenal tissue.

We have been unable to make a satisfactory diagnosis—many questions require answers first. Are the endometrial scrapings those of severe estrin type of hyperplasia associated with multiple follicular retention cysts, or are they adenocarcinoma? There was no evidence of cell invasion.

Uterine bleeding of hyperplasia endometrii is not usually seen in women having hypertrichosis and macroclitoris. Moreover hypertrichosis and an enlarged clitoris are almost invariably associated with scanty periods, generally with amenorrhea. In

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ARSENICAL ENCEPHALITIS DURING PREGNANCY

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A RARE but often fatal reaction resulting from arsphenamine administration in the treatment of syphilis in pregnancy is hemorrhagic encephalitis.

A review of the literature from 1912 to 1937 showed this condition to be fatal in 29 pregnant women. In a series of 17,000 arsphenamine injections given at the University of Pennsylvania Hospital, the only death reported occurred in pregnancy. During the ten years prior to 1927, Kristjansen of the Rudolph Boegh's Venerological Hospital in Copenhagen reported three deaths in pregnant women. In our obstetric service, which handles approximately 1500 cases a year, only two cases of hemorrhagic encephalitis following arsenical administration have recently occurred. We wish to report these two cases.

CASE 1.—M. M., a 34-year-old white female, was admitted to the hospital in June, 1937, with the symptoms of dyspnea, dizziness, and inability to walk. There was a red macular rash over the entire body. Previous to admission she had received neoarsphenamine injections for syphilis at the Dispensary. Nine days before the onset of her symptoms she had received her first injection of the drug. Her past history revealed the usual childhood diseases. She had had six pregnancies, of which the first five were normal full-term deliveries. All five children are living and well. Her sixth pregnancy was a one and one-half month abortion induced by the patient with ergot. At the onset of her present illness the patient was approximately eight months pregnant. The course of the present pregnancy had been normal, and the estimated date of confinement was July 12, 1937. A routine examination of the blood at the Dispensary gave a positive Wassermann reaction, and the patient was advised to submit to antisyphilitic therapy.

The physical examination revealed a well-developed, well-nourished white female with audible inspiratory and expiratory dyspnea. The tongue was markedly swollen. Her pupils were round and equal and reacted to light. No nystagmus was noted. The examination of the heart and lungs revealed no pathology. The abdomen presented the aspect of an approximately eight-month pregnancy. The position of the fetus was back to the left and occiput anterior and a cephalic presentation. The fetal heart sounds could be heard but the rate was not determined. The patient showed a red macular rash over the extremities and abdomen. The biceps, triceps, and patellar reflexes were exaggerated. The Gordon, Oppenheim, and Babinski reflexes were positive.

Laboratory Findings.—The Wassermann reaction, which had been positive when examined at the antepartum clinic, was negative in the hospital. The hemoglobin content was 14.6 gm.; the red blood cells numbered 3,900,000; the white blood cells numbered 13,250. The differential count showed 70 per cent segmented polymorphonuclear leucocytes and 16 per cent were immature leucocytes; 6 per cent were lymphocytes; 4 per cent were monocytes and 4 per cent myelocytes. The number of platelets was 296,400. The urine was 1.040, acid, albumin content 20 mg. per cent, and a positive reaction for sugar and acetone. Microscopically a moderate amount of red blood cells, numerous white blood cells, and hyaline, granular, and cellular casts were noticed. The spinal fluid showed on her third hospital day an increased pressure of 140 to 200 mm. of water. On her fourth hospital day the pressure rose to 340 mm. of water. The spinal fluid was clear, the cell count was not increased; there was a positive globulin reaction and the colloidal gold curve was normal. The Wassermann and Kahn reactions were negative.

a search of literature I have found no case in which virilism and such profuse bleeding were concomitant.

It is possible that there be an hypertrophy of Grollman's androgenic layer of the adrenal sufficient to cause masculinization without causing an enlargement of the adrenal bodies great enough to detect its presence this side of an adrenal biopsy. However, such hypertrophy is usually accompanied by a marked and rapid increase of weight. Our patient had little weight change aside from the loss of a few pounds which she regained postoperatively. Basophilic adenoma of the pituitary is accompanied by hypertrichosis and sometimes clitoral hypertrophy, but the skin striae, the hypertension, the osteoporosis, and the obesity, also of Cushing's syndrome, are absent in our patient.

Perhaps the pituitary condition, which is believed to stimulate the formation of multiple follicles, also stimulates the androgenic tissue of the adrenals, each hormonal influence being sufficiently strong to maintain its specific effect. Yet we are used to thinking of the male or female factor as dominant; even in hermaphrodites one type of secondary sex characteristics rules.



Fig. 2.

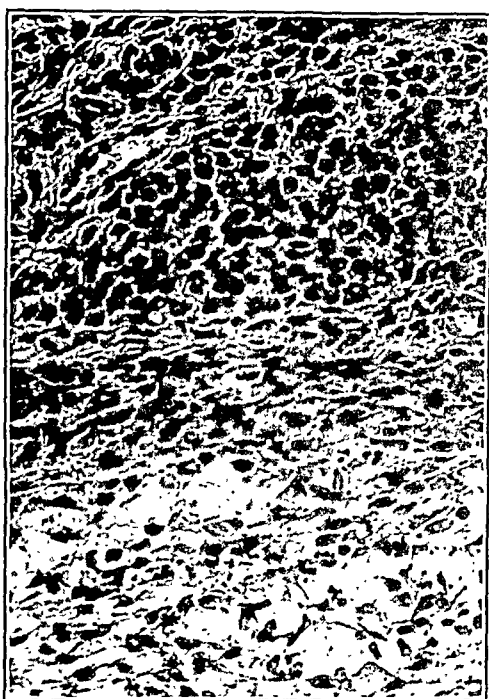


Fig. 3.

Fig. 2.—Low-power of ovary showing a definite attempt toward the formation of a structure. Three such places are visible. The one marked with the arrow is the entity selected for the high power microphotograph in Fig. 3.

Fig. 3.—High power of wall of peculiar area seen in Fig. 2.

Still remains the problem of the structures seen in the yellowish part of the ovaries. Perhaps the theca lutein-like cells impart the yellow color. We have no experience with xanthrofibroma folliculare which W. Schiller mentioned in the December, 1936, number of the *Journal of Obstetrics and Gynaecology of the British Empire*. He speaks of it as an unripe cellular fibroma, varying from the size of a hazelnut to a fist, permeated by small lipoid droplets and says that clinically it causes mechanical symptoms of fibroma, yet the fat which it produces and stores has an hormonal character which may at times cause hyperplasia of the mucosa and bleeding. He furthermore notes amenorrhea can also occur, because the elements of the tumor are luteinized connective tissue of the ovary. We have been unable to find further references, and we can only see faint resemblance to this entity in the peculiar structures of these ovaries. Nevertheless, one does not forget the close relation of the chemical structure of sterols and the sex hormones.

to the right and occiput anterior and a cephalic presentation. The fetal heart sounds could be heard in the lower right quadrant, and the rate was 140. The patient was not in labor. The rectal examination revealed the fetal head well above the rim of the pelvis, and there was no dilatation of the cervix present. The biceps, triceps, and patellar reflexes were increased. The Babinski, Gordon, and Oppenheim reflexes were positive. Ankle clonus was not present; neither was the Chaussek's nor Trousseau's sign present. There seemed to be a spastic type of paralysis of the upper extremities. The forearms were flexed upon the arm and could be straightened out only with the greatest difficulty. It was impossible to perform any laboratory work on this patient due to the rapid and fatal course of the disease.

On admission the patient was excited and restless and could not speak. Her respirations were stertorous and labored, and her pulse rapid but of poor volume. There was profuse diaphoresis present; her skin was cold and clammy. Her blood pressure at this time was 100-70, and the fetal heart sounds were 140. Later during the night the patient's finger nails, ear lobes, and lips became cyanotic. An acute laryngeal edema seemed to develop, and an emergency tracheotomy was performed.

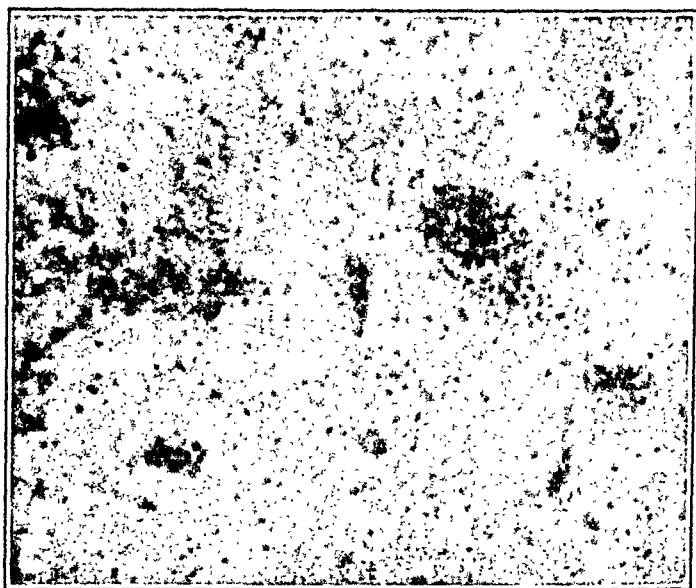


Fig. 1.—Microscopic picture of the hemorrhagic encephalitis. (Haem-eosin $\times 120$.)

After the operation the respirations seemed less labored. The pulse had increased to 128 beats per minute; the volume was still poor. A large amount of mucus accumulated in the mouth due to her inability to swallow, and made the use of a suction apparatus necessary. At this time the patient was in deep coma. Her temperature rose to 105.6° F. At this time fetal heart sounds were still audible and the rate was 140. The patient's condition remained the same during the night until early in the morning, at which time the respirations became rapid and shallow, the pulse weak and irregular, and the temperature rose to 107.8° F. Soon the pulse became faster and the patient died under gasping respirations and deep cyanosis. A post-mortem cesarean section was done immediately, and a normally developed stillborn baby was delivered.

Our therapeutic effort during her brief illness consisted chiefly in the administration of various sedatives, heart stimulants, oxygen, emergency tracheotomy, and sponge baths.

Summarizing briefly the important features of the above history, we may state that the patient apparently developed an acute and rapidly progressive lesion in the medulla oblongata, causing death by respiratory paralysis. The severe coma, the lateral nystagmus, the increased reflexes and positive signs, incoherent moving of the extremities with clonic contractions of the muscles pointed definitely to diffuse

On admission the patient was restless but rational. Her respirations were stertorous, her tongue thick, and her pulse was rapid and of poor volume. She had involuntary micturition. During the following day her temperature rose and the pulse rate increased to 140. The rate of the respiration was 40. During the night swallowing became difficult and the respirations were labored and shallow. The patient at this time refused anything by mouth. On the third day muscle twitching could be noticed in the extremities. The patient at this time was in a deep coma, her temperature rose to 103.7° F., and she was perspiring profusely. Due to her inability to swallow, a large amount of mucus then accumulated in the mouth and made the use of a suction apparatus necessary. At this time no more fetal heart sounds could be heard, which indicated death of the fetus. On the fourth day the patient roused for a short period from her coma, but her pulse rate and temperature rose to 105.8° F., and cyanosis began to become manifest. Towards the same evening she developed Cheyne-Stokes type of respirations. Her pulse became rapid, weak, and irregular, and she died the afternoon of the same day.

During her six days of illness our therapeutic efforts consisted chiefly in the administration of sodium thiosulfate, various sedatives, heart stimulants, and the parenteral administration of saline, sucrose, and magnesium sulfate.

Summarizing briefly the important features of the above history, we may state that the patient apparently developed an acute and very progressive lesion involving chiefly the respiratory center in the medulla oblongata causing death by respiratory paralysis. While no definite localizing brain symptoms were present at any time, the severe coma, the involuntary micturition, incoherent moving of the extremities with clonic contractions of the muscles and increased reflexes pointed definitely to extensive involvement of the brain. The albumin in the urine in the absence of acute congestion can be taken as evidence of toxic damage to the kidney parenchyma, and the appearance of the macular rash at the onset of the disease led us to establish the clinical diagnosis of acute arsenical intoxication following administration of neoarsphenamine.

CASE 2.—B. H., a 24-year-old white female, admitted to the hospital in July, 1937, with the symptoms of inability to speak, inability to breathe properly, vomiting, and sore mouth. Previous to admission she had been receiving neoarsphenamine injections for syphilis. Seventeen, ten, and three days before admission she had received her first three injections of the drug. The day before her last injection she had complained of nausea and had vomited twice during the same day. The day of her last injection she was nauseated and vomited persistently since the time of injection. During the evening of the same day she first noticed difficulty in speaking.

Her past history revealed the usual childhood diseases. She had had three pregnancies, of which the first was a miscarriage, the last two normal full-term pregnancies. Both children are living and well.

At the time of her present illness the patient was approximately eight months pregnant. The course of this pregnancy had been normal and the estimated date of confinement was August, 1937. The Wassermann reaction of her blood was strongly positive, and antisyphilitic treatment was started at the dispensary.

The physical examination revealed a well-developed and well-nourished white female with audible inspiratory and expiratory dyspnea. The expiratory rate was 30 per minute. There was a definite lateral nystagmus present. The pupils were unequal in size but did react to light and accommodation. There was a severe pallor around the nose and mouth. Upon inspiration the nostrils were drawn into the septum. The breathing was harsh and loud and the auxiliary respiratory muscles had to be used by the patient to get sufficient air. The mucous membrane of the mouth was pale and the tongue was heavily coated. The breath was foul. There were uncontrolled movements of the arms and legs. No clonic or tonic contractions were present. The patient seemed dazed and could not answer questions; however, occasionally she would indicate answers with her fingers. The examination of the heart and lungs revealed no pathology. The abdomen presented on examination an approximate eight months' pregnancy. The position of the fetus was back

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ACTINOMYCOSIS AND BLASTOMYCOSIS OF FEMALE GENITALIA

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IT IS a common belief that mycotic infections of the female pelvic organs are rare. To date 77 cases of actinomycosis have been recorded, the last by Lisa and Levine,¹ who gave references for all previously reported cases.

The only reports in recent years of blastomycosis affecting the female genitalia were by Ocana,² which affected the cervix uteri, and by Perazzi,³ which was vulvo-vaginal in distribution. The latter can be considered comparable to cutaneous blastomycosis, which cases are common, next to which in occurrence are systemic and pulmonary cases. Single cases of blastomycosis affecting the urethra, kidney, bladder and prostate have been reported respectively by Preis and Foro,⁴ Tepel,⁵ Rhamy,⁶ and Lewis, Carroll, and Stryker.⁷

The recent findings of a case of actinomycosis and another of blastomycosis are submitted as records to further the conception that mycotic infection of the female genitalia is probably more common than is realized.

ACTINOMYCOSIS

A. V., a young, white woman, aged 29 years, married and the mother of one child, born five years ago, was admitted to the hospital on Oct. 11, 1933, and gave the following history:

Shortly after the birth of this only child, she began to complain of pain in the right lower abdomen and was quite sick for several weeks in a hospital in Bayonne, N. J. At this time, she had a high temperature and for a time was "out of her mind." After recovering from this acute post partum period, she suffered continuously with pains in the right side, associated with nausea, vomiting, and poor appetite. The pains were always aggravated during menstruation. Her family history as well as her past history are entirely negative and have no bearing on her present illness. On examination, she appeared to be a well-nourished, young woman with good healthy color. The findings, aside from the lower abdomen were essentially negative. The abdomen revealed nothing above the umbilicus, but there was definite tenderness with some rigidity in the entire lower abdomen. Bimanual examination showed particularly marked tenderness in the right fornix and a definite palpable mass which was firm and adherent. A diagnosis of chronic pelvic inflammatory disease was made, apparently originating at the time of her delivery.

involvement of the brain. The symptoms, history, and physical findings, and the fact that one previous case had similar findings suggested to us the clinical diagnosis of acute arsenical intoxication following administration of neoarsphenamine. The autopsy findings confirmed our clinical diagnosis.

The detailed pathologic description of the cranial cavity and its contents is as follows: The superficial aspects of the cerebral hemispheres presented a marked congestion, a slight thickening of the meninges along the vessels, and a moderate softness of the brain substance. The consistency was apparently the same in both cerebral hemispheres. The spinal fluid was slightly blood-tinged, and there was slight congestion of the walls of the lateral ventricles. There was marked congestion of the white matter of the brain and a few petechial hemorrhages were present. On cut section the pons revealed a marked softening and swelling with numerous small, discrete and confluent petechiae involving the entire cross section of the pons. The pathologic evidence found in the pons and the immediate surrounding structures presented a general aspect of hemorrhagic myelitis, probably of the arsenical type. Multiple sections through the brain stem revealed no involvement of the medulla or cervical cord. There were, however, bilateral areas of softening and diffuse pink staining of the thalamus bilaterally.

From these pathologic findings the anatomic diagnosis of acute hemorrhagic encephalo-myelitis was made. Other pathologic findings at the autopsy table included a slight atheromatosis of the aorta, fatty changes of the myocardium, parenchymatous degeneration of the liver and kidneys, dilatation of the ureter, chronic pelvic peritonitis with adhesions, and a slight anemia.

The histopathologic examination of various sections of the brain showed small petechial hemorrhages scattered throughout the entire brain but being most remarkable in the pons. There extensive destruction of the nerve substance by confluent and profuse hemorrhages could be noted. The vessels of the brain showed dilatation with hyperemia. The Virchow-Robin spaces were filled with blood which penetrated in the form of fine streaks into the surrounding nervous tissue. No infiltration with leucocytes could be noted. The ganglion cells of the cortex of the brain appeared slightly swollen with deep purple staining protoplasm.

CONCLUSIONS

A more constant supervision of the pregnant woman who is under arsphenamine therapy during the second and third trimesters is urged. The onset of hemorrhagic encephalitis is so insidious that the routine laboratory tests are of little diagnostic value. Constant questioning of the patient before each treatment in order to detect any evidence of early arsenical reaction may help to discover any toxic reaction to the drug.

A thorough history of the patient with reference to disease of the heart, kidneys, and lungs may call for special laboratory tests to check the function of these organs before the institution of arsenical therapy. Due to the rarity of this condition, it is not feasible to withhold arsphenamine treatment in pregnant syphilitic individuals.

Smaller doses of the arsenicals, given at weekly intervals, are indicated in the latter half of pregnancy. A constant check of the general health of the patient under treatment, with frequent examinations of the urine, appears to be the only means of preventing this serious treatment reaction in pregnant women.

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but with plasma cells predominating. Between the tubal and ovarian structures were binding masses of fairly loose, newly formed fibrous tissue and the adjacent ovarian structure appeared unaffected. In other places the ovarian structure was affected by small areas being densely occupied by polymorphonuclear leucocytes and plasma cells, in about equal proportion. In none of these areas of the ovarian tissue were found any masses of actinomyces as observed in the tube. In the outer border of the affected tissues were extensive areas of newly formed fibrous tissue, into most of which were scattered many of the inflammatory cells. The vascularity showed but little increase.

The masses of actinomyces showed little morphologic structure in sections stained by hematoxylin and eosin, except for a few mycelial filaments projecting at the margin. By Gram stain the periphery had many intertwined gram-positive hyphae. The central portion was gram-negative and resembled a mass of densely packed amorphous granules, none of which showed any suggestion of a crystalline structure.

Appendix showed obliteration of the lumen and no evidence of any other pathologic change.

Her postoperative period represented a very normal convalescence for the first five days. The drainage was a dark serous material. On the fourth day, she felt nauseous and vomited. On the fifth day, her temperature began to rise, reaching a maximum of 101.6° F. on the seventh day and then gradually came down by lysis, returning to normal on the thirteenth day.

On the fifth day, she became irrational and was very drowsy. She had periods of excitation and hyperactivity and had to be restrained. On the eighth day, she had a fine reddish rash on her chest and arms suggesting a bromide rash. Also, there was some purulent discharge from the wound.

After thirteen days, her mental condition returned to normal, the wound cleared and she made an excellent recovery. The mental disturbance, according to her husband, was similar to the one she suffered following the birth of her child.

This patient was followed for six months after the operation, since when it has been impossible to locate her. For the time observed, she enjoyed excellent health.

BLASTOMYCOSIS

M. P., a young, white woman, aged 29 years, was admitted to the hospital on Jan. 16, 1934, with the following history:

For the past four years, she had had pelvic pain, bearing down, numbness in the right leg with headache, indigestion, and backache. She never had leucorrhea. Lately, she had some nausea, vomiting and chronic constipation. She was married at the age of 18 years, living with her husband for one year. She married the second time a man about ten years older than herself and lived with him for three years. Her menses appeared every five to six weeks, lasting ten days. Occasionally, she had a period in between, but the flow was usually scant. Physically, the patient appeared well-nourished and of good color. Examination was essentially negative, except that on vaginal examination there was revealed a large, nodular, immovable uterus, suggesting multiple fibroids.

Operation on Jan. 17, 1934, through a midline incision, revealed a mass consisting of the left tube and ovary, surrounded by the rectum. The right tube was behind the uterus, about the size of a lemon. The appendix was apparently adherent and involved in the mass on the right side, between the tube and the cecum.

The left tube and ovary were removed en masse. The right tube and apparently the remnant of the appendix, were also removed. The numerous adhesions were separated and after suturing the fundus of the uterus to the peritoneum, a cigarette drain was placed in the pouch of Douglas and the abdomen was closed.

Laboratory Findings.—Urine was negative except for very faint trace of albumin. Culture from operative area; no bacteria.

Pathologic Examination.—Specimens consisted of right tube and left tube and ovary. Right tube measured 7 cm. by 3 cm. by 2 cm. External surfaces are pale and dull. Cut surfaces showed thick, firm, pale walls and lumen slightly distended with thick, creamy fluid. The distal end was closed. Left tube and ovary appeared fused together into a single large mass, measuring 6 cm. by 5 cm. by 4 cm. External

At operation on October 11, a right pararectus incision was made. The appendix was not immediately visible, but in the right pelvis a large, dense, adherent mass was found. It was closely fused with the uterus and a loop of the ileum. This was carefully separated and found to be the site of an old abscess with a mass about the size of an apple, involving the right tube and ovary and the right cornu of the uterus. All of this diseased tissue was completely excised. The left ovary was left in situ after puncturing a few small cysts. The appendix was small and atrophic, but surrounded by adhesions. It was removed. The abdomen was then closed with a cigarette drain to the pouch of Douglas.

Laboratory Findings.—Oct. 11, 1933. Urine normal except for a faint trace of albumin; W.B.C., 8,800; polymorphonuclear neutrophils, 58 per cent; eosinophiles, 3 per cent; monocytes, 2 per cent; lymphocytes, 37 per cent. Culture from operative area shows pure growth of *Staphylococcus aureus*. Oct. 17, 1935. W.B.C., 19,650; polymorphonuclears 84 per cent; eosinophiles, 1 per cent; monocytes, 2 per cent; lymphocytes, 13 per cent.



Fig. 1.



Fig. 2.

Fig. 1.—Case 1. Actinomycotic mass in the Fallopian tube. Gram stain, showing marginal filaments gram-positive and central granular mass gram-negative. $\times 65$.

Fig. 2.—Case 1. Margin of actinomycotic mass in the Fallopian tube, showing gram-positive filaments and granular center. $\times 700$.

Pathologic Report.—Specimens consisted of right Fallopian tube and ovary together, the left tube and the appendix. Right tube measured 10 cm. in length and 2 cm. in greatest diameter. The distal end was closed. Serous surfaces were pale, dull, and smooth. Cut surfaces showed thick, pale, firm walls and large lumen filled with thick, creamy fluid. Right ovary measured 4 cm. in greatest diameter. It was oval in shape and externally encircled by the tube, which was firmly adherent to it. Cut surfaces showed pale, firm tissue with numerous small round cysts just beneath the exposed surfaces. Left tube measured 5 cm. in length and appeared normal. Fimbriated extremity was patent. Appendix measured 2.5 cm. in length and 0.3 cm. in almost uniform diameter. Cut surfaces showed pale firm structure and no evidence of a lumen.

Microscopic Examination.—The right Fallopian tube had the lumen distended and the walls thinned by the purulent contents, consisting mostly of polymorphonuclear leucocytes but with a high proportion of plasma cells and less so of lymphocytes, among which were found small masses of actinomyces (Figs. 1 and 2). Many of the strands of muscle tissue in the walls were separated by collections of similar cells

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A FIVE-YEAR STUDY OF ECLAMPSIA IN MARYLAND

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IT HAS often been reported that the incidence of eclampsia in the State of Maryland is unusually high. These reports were principally based upon the work of Williams¹ in 1912. This study has been undertaken to find if this assumption is still justified, and at the same time to investigate other aspects regarding the disease in this State.

Medical literature provides considerable data on eclampsia. There are wide variations in incidence and mortality throughout the world. In the United States both incidence and mortality are about the average; however, it is estimated² that today eclampsia and the toxemia associated with it accounts for 30 per cent of the approximately 15,000 annual maternal deaths in this country. Therefore, as Bill³ states, eclampsia still remains our greatest problem in obstetrics.

Table I gives a brief statistical review of eclampsia in various regions of the world. It is mostly based upon hospitalization rather than on the total number of births occurring in the given area, and probably accounts for the wide variation.

Our period of study includes the five years from 1931 through 1935. It is difficult to obtain complete information about eclampsia in Maryland as no report of the disease is made to the Health Department except when death occurs. As most cases of eclampsia in Maryland are hospitalized, it was felt that by examining the records of all hospitals in this state we could obtain nearly the complete incidence of eclampsia which occurred in pregnancies for the period. A questionnaire was made up and sent to each of the 34 hospitals taking care of maternity cases. One of the authors personally visited 14 of these hospitals and examined their records, while 18 others responded satisfactorily to the questionnaire. Two small hospitals in outlying sparsely settled districts failed to respond; however, it is our impres-

surfaces were dark red and rough. Cut surfaces showed thick, firm, pale walls, and the lumen was distended and closed off into several cystic cavities filled with thick, creamy fluid.

Microscopic Examination.—Both tubes were densely filled with polymorphonuclear leucocytes and almost as many plasma cells. These same cells extended into the walls between the strands of muscle. Beyond these the ovarian tissue was attached by extensive fibrous tissue in which were many plasma cells, some lymphocytes and a few polymorphonuclear leucocytes. The surrounding ovarian stroma showed considerable increase in dense fibrous tissue. In the tissue from the right side it was impossible to identify any portion of the appendix. Direct examination of unstained contents of the tubes showed the presence of some budding yeast cells. Inoculation upon Sabouraud's media shows growth of budding yeast cells and also mycelia with arthrospores and conidia (Fig. 3). Subcultures give variations in appearances of the colonies with considerable tendency to early pleomorphism. All the colonies present a tough, dark brown, leathery mass, which is also a distinctive characteristic of blastomyces.

Her postoperative course was uneventful. She made an excellent recovery and was discharged from the hospital on Feb. 3, 1934, and has enjoyed fine health to the time last seen which was in September, 1936.

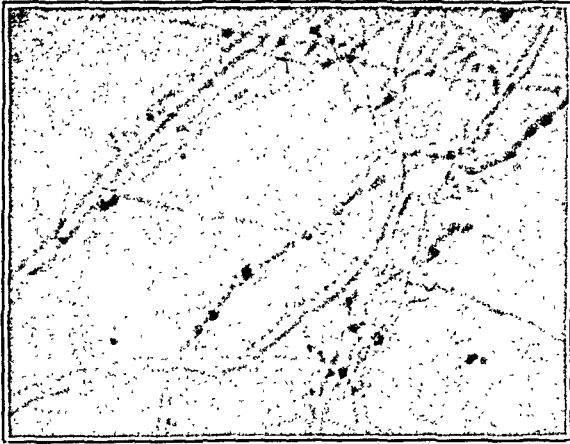


Fig. 3.—Case 2. Blastomyces cultured from budding yeast cells found in pyosalpinx. Unstained. $\times 700$.

DISCUSSION

Most cases of mycotic infection of the female genitalia have been reported originating by extension from the gastrointestinal tract. In the actinomycosis case there is nothing to support such an origin, and it can be considered to have occurred by way of the genital tract following delivery, as in the case cited by Junghans.⁸ The blastomycosis case evidently occurred by extension from the appendix to the right tube and ovary between which there was such a massive lesion that the appendix as part of the tissue removed was not recognized.

The 71 cases of actinomycosis of female genitalia listed by Cornell⁹ were classified as follows: cured 11, improved 8, doubtful 7, died 45. To this may be added three cured cases: Gardiner,¹⁰ Lisa and Levine,¹ and the one herein cited; and three fatal cases, two of Counsellor and Hoerner,¹² and one of Junghans.⁸

The two types of fungi here cited are widely different from each other in their characteristics. Their classification among the other fungi is given by Castellani¹³ and Henrici¹⁴ who state the actinomyces as being closely related to the mycobacteriaceae and bacteria, especially the acid fast types. Both classify the other organism, blastomyces, under the fungi imperfecti and Castellani¹⁵ applies the name blastomycoides to it, discarding the term blastomyces and using that of blastomycosis for the yeasts (saccharomyces) and the three yeastlike organisms (cryptococcus, or torula, monilia and endomyces).

sion that they do little or no obstetrics and their failures are relatively unimportant, affecting the final figures very little.

INCIDENCE FOR THE PERIOD OF STUDY

During the five-year period, 139,618 live births and 8,712 stillbirths were recorded in the State.²⁶ If correction is made for sets of twins (1,650) and triplets (914), the number of pregnancies represented by these births and stillbirths would be 146,652. Among these there were 299 cases of eclampsia or an incidence of 1 case in 490 pregnancies (0.20 per cent). Of the 299 cases, 69 occurred in 1931, 50 in 1932, 74 in 1933, 47 in 1934, and 59 in 1935. There is no significant variation in the number of cases appearing yearly.

PARITY

In the present series, 70.5 per cent were primigravidas and 29.5 per cent multigravidas (Table I). Of the 146,652 pregnancies, 46,428 were primigravidas and 100,224 were multigravidas. The incidence of eclampsia for primigravidas therefore, was one in 220 pregnancies or 0.45 per cent and for multigravidas one in 1,139 or 0.09 per cent. These results bear out the well-recognized fact that eclampsia is much more prevalent in the primigravidas.

RACE

The large negro population of Maryland made it possible for us to study the problem on a racial basis. One hundred and seven of the 33,155 colored pregnant women had eclampsia or one in 310 (0.32 per cent) as compared to one in 591 (0.17 per cent) in the white race. The prevalence of eclampsia in the negro is in agreement with the findings of Upshaw¹¹ in Georgia who reported an even greater incidence of 1.5 per cent, and it can partly be explained by the lack of prenatal care, age, and poor living conditions of these people. Table II gives a further comparison subdivided according to multiparous and primiparous pregnancies.

TABLE II. INCIDENCE OF PARITY BY RACE

	WHITE			COLORED		
	PREGNANCIES	CASES	INCIDENCE PER CENT	PREGNANCIES	CASES	INCIDENCE PER CENT
Primigravidas	37,724	136	0.36	8,704	75	0.86
Multigravidas	75,773	56	0.07	24,451	32	0.13
Total	113,497	192	0.17	33,155	107	0.32

TYPE OF ECLAMPSIA

One hundred and sixty-four or 54 per cent of the cases occurred ante partum, 75 or 25.4 per cent intra partum, and 60 or 20 per cent post partum. These figures coincide with most authors and very closely approximate the series studied by Williams.¹ The percentage of cases appearing ante partum and intra partum in the primigravidas and the multigravidas are about the same. Post partum eclampsia is 7 per cent more common in the multigravidas (Table III).

TABLE III. DIVISION OF CASES AS TO TYPE AND PARITY

	ANTE PARTUM		INTRA PARTUM		POST PARTUM	
	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL	NO. OF CASES	PER CENT OF TOTAL
Primigravidas	118	55.8	55	26.0	38	18.2
Multigravidas	46	52.2	20	22.7	22	25.1
Combined	164	54.6	75	25.4	60	20.0

TABLE I. RÉSUMÉ OF CASES REVIEWED IN LITERATURE*

YEAR	AUTHOR	REGION	NUMBER OF LABORS	NUMBER OF CASES	% INCI- DENCES	% PRIMI- GRAVIDA	% MULTI- GRAVIDA	% ANTE PARTUM	% INTRA PARTUM	% POST PARTUM	% MATERNAL MORTALITY	% FETAL MORTALITY
1912	Williams ¹	Baltimore	11,000	110	1.00	60.0	40.0	55.5	22.7	21.8	22.8	44.5
1922	McPherson ⁴	New York	120,000	890	0.75	64.4	35.6	65.0	20.0	15.0	17.4	25.4
1922	Cruikshank ⁵	Glasgow	23,630	814	3.44	65.1	34.9	78.5	---	21.5	22.4	36.6
1926	Greenhill ⁶	Chicago	29,587	83	0.28	73.1	26.9	50.0	20.5	29.5	7.7	27.7
1926	Davis ⁷	New York	152,248	879	0.57	N.R.	N.R.	58.0	13.4	28.6	23.0	34.0
1927	Rice ⁸	New York	42,070	222	0.53	58.0	42.0	50.0	23.0	27.0	21.0	45.0
1930	Gyllensvärd ⁹	Stockholm	48,053	232	0.60	N.R.	N.R.	N.R.	N.R.	N.R.	7.8	31.0
1930	King ¹⁰	Peiping	2,256	33	1.50	75.0	25.0	60.0	30.0	10.0	12.1	44.0
1930	Upshaw ¹¹	Georgia	9,730	152	1.50	68.0	32.0	84.0	---	16.0	21.0	34.0
1930	Stapleton ¹²	Calcutta	1,200	65	5.40	81.5	18.5	18.0	75.8	6.2	22.0	N.R.
1932	Hoffstrom ¹³	Finland	25,260	240	0.95	80.0	20.0	N.R.	N.R.	N.R.	15.9	29.8
1932	Gerrard ¹⁴	England	9,116	100	1.09	72.0	28.0	43.0	29.0	18.0	7.0	N.R.
1933	Gibson ¹⁵	Australia	16,903	101	0.61	68.1	31.9	59.0	20.0	21.0	8.9	36.0
1934	Hauch ¹⁶	Denmark	737,701	1,286	0.17	N.R.	N.R.	N.R.	N.R.	N.R.	15.5	34.1
1934	Binder ¹⁷	New Jersey	18,942	123	0.70	N.R.	N.R.	31.7	31.7	36.6	11.4	44.3
1936	Kimbrough ¹⁸	Philadelphia	12,601	43	0.34	80.0	20.0	65.2	9.8	25.0	13.9	28.0
1937	Reese and Peyton	Maryland	146,652	299	0.20	70.5	29.5	54.6	25.4	20.0	20.4	31.0

*N. R., Not reported.

this study were treated in both ways, the conservative method increasing as time went on. So far as could be determined there were few, if any, variations from the accepted methods of sedation, rest, etc., in those cases so handled. One hundred and eight or 45.7 per cent of the 239 patients having ante- and intra-partum eclampsia were treated radically, the remaining 131 conservatively. Primigravidas were more often treated by hastening the termination of pregnancy than multigravidas, the percentages being 47 and 30 per cent, respectively.

In comparing Baltimore, the only large city in the State, with the rest of the state, an interesting finding was obtained. Table V shows the number of patients treated in Baltimore as compared to the rest of the state and the method of treatment for the patients having eclampsia before delivery. Twenty-seven per cent of the patients were treated radically in Baltimore in contrast to 65 per cent treated in the same way in the rest of the state.

TABLE V. TYPE OF TREATMENT BY LOCATION FOR ANTE- AND INTRA-PARTUM ECLAMPSIA

LOCATION	NO. OF CASES	TREATMENT	
		RADICAL	CONSERVATIVE
Outside of Baltimore	108	71	37
Baltimore	131	37	94

MATERNAL MORTALITY

Sixty-one of the 299 patients died giving a mortality of 20.4 per cent. This mortality rate is higher than in certain regions in the United States but is 10.5 per cent less than the report of 1912 for Baltimore.¹ The number of deaths in this study represent 8.3 per cent of the total 737 maternal deaths in the States for the period.^{2*} We have accounted for 61 of the 70 deaths reported as eclampsia on death certificates.

Forty-three or 71 per cent of the deaths were in the ante-partum eclamptic patients while 17 per cent and 12 per cent were in the intra- and post-partum cases, respectively. The mortality rates are shown in Table VI; post-partum eclampsia in multigravidas appear to be most fatal.

TABLE VI. MORTALITY RATES FOR THE CASES AS TO PARITY AND TYPE

GROUP	ANTE PARTUM	INTRA PARTUM	POST PARTUM	TOTAL
Primigravidas	24%	15%	2.7%	14%
Multigravidas	20%	12%	32%	28%
Combined	26%	13%	13%	20%

Surgical treatment increased the maternal mortality tremendously. Thirty-four per cent of all patients treated radically died, in contrast to 12 per cent

TABLE VII. REGIONAL MORTALITY OF CASES BY TREATMENT

LOCALITY	TREATMENT*					
	SURGICAL			MEDICAL		
	NO. CASES	NO. DEATHS	MORTALITY	NO. CASES	NO. DEATHS	MORTALITY
Outside of Baltimore	71	26	36%	40	7	27%
Baltimore	37	11	33%	91	9	10%
Maryland (Total)	108	37	34%	131	16	12%

*Post-partum eclampsia was not included in these figures.

MULTIPLE PREGNANCY AND ECLAMPSIA

Crowe¹⁹ and others^{6, 11, 15, 18} report that from 4 to 7 per cent of their cases of eclampsia were associated with multiple pregnancy. In this series there were 9 multiple pregnancies or one out of every 30 (3 per cent), and since the normal incidence of twin pregnancy is usually given as one in 80, it could be assumed that eclampsia is $2\frac{1}{2}$ times as prevalent here as in single pregnancies.

RECURRING ECLAMPSIA

In recent years more has been written about the recurrence of eclampsia. Peckham²⁰ reports that at Hopkins 4 per cent of all eclamptic patients suffer from a second attack in a future gestation; Young²¹ in Edinburgh, cites various authors' findings as being from 1.5 to 2.8 per cent. Schmeckel finds that in Dresden 40 per cent of eclamptic patients have symptoms and 20 per cent develop convulsions in future pregnancies. The latter author states that in a recurring case the disease is benign. We found eclampsia recurring in 5 cases. Four of the cases were of the severe type and 3 patients died, making the mortality 60 per cent. We believe the physician should consider the pregnant woman with a history of eclampsia seriously. If a second attack has occurred, we recommend prevention of future pregnancies, and if she becomes gravid for the third time, and shows evidence of severe kidney dysfunction, we recommend abortion.

SEVERITY OF ECLAMPSIA

Each case of eclampsia was designated severe or mild depending upon the number of convulsions or coma. Ten or more convulsions or prolonged coma classified a case as severe. One hundred and nineteen or 40 per cent of all the cases were of the severe type, and ante-partum eclampsia appeared to be the most severe. The cases are compared according to severity and parity in Table IV.

TABLE IV. SEVERE AND MILD CASES ACCORDING TO PARITY AND TYPE

	ANTE PARTUM		INTRA PARTUM		POST PARTUM		TOTAL	
	SEVERE	MILD	SEVERE	MILD	SEVERE	MILD	SEVERE	MILD
Primigravidas	55	63	15	40	11	27	81	130
Multigravidas	23	23	4	16	11	11	38	50
Combined	78	86	19	56	22	38	119	180

TREATMENT

Probably no other obstetric complication has been given as much consideration as the handling of the eclamptic patient. There have been for the past twenty years two distinct schools of treatment: conservative and radical, the former gaining in followers as time goes on, and showing upon the whole decidedly better results for the mother, and apparently fairly good for the baby. The patients in

NUMBER OF CASES TREATED CONSERVATIVELY AND RADICALLY BY YEAR



7. Recurring eclampsia is severe and carries a high mortality.
8. Ante-partum eclampsia is the most severe type.
9. Forty-six per cent of the patients suffering from eclampsia before delivery were treated radically.
10. The total maternal mortality was 20.4 per cent.
11. Post-partum eclampsia in the multigravida is most fatal with a mortality of 32 per cent.
12. Cases handled conservatively had a mortality of 12 per cent in contrast to 34 per cent for those treated radically.
13. The total fetal mortality was 30.2 per cent and the risk for the baby is greater if mother receives conservative treatment.
14. The desired grade of prenatal care is outlined.
15. Fifty-four per cent of the patients receive no prenatal care. Very few receive adequate care.
16. Early detection and control of the preeclamptic is the means of attacking eclampsia.
17. Both incidence and mortality of eclampsia are diminished by adequate prenatal care.

The authors desire to thank the various hospitals for their cooperation in this study and the Baltimore City Health Department for the general statistics furnished.

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Goedel, R.: Roentgen Ray Treatment of Puerperal Mastitis, Strahlentherapie 58: 651, 1937.

The treatment of choice in cases of acute mastitis is roentgen ray therapy, applied early and repeated at definite intervals. In this way operation may be avoided in almost 100 per cent of cases, recurrences are prevented and nursing is maintained.

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mortality for those receiving conservative therapy. Table VII reveals the analysis of cases as to treatment in Baltimore and the rest of the State with their respective mortalities.

FETAL MORTALITY

Ninety-three of the 308 babies (includes 9 sets of twins) were stillborn or died within seventy-two hours. This gives a total fetal mortality of 30.2 per cent. Only two babies whose mothers had post-partum eclampsia died, giving a fetal mortality of 36 per cent for those patients developing eclampsia prior to delivery. This figure is much lower than the average for the world, and approximates the record of clinics reporting the lowest mortality rates. Prompt surgical treatment of the mother was followed by a 17 per cent fetal mortality, while those patients treated conservatively showed a 43 per cent fetal mortality indicating that the risk for the baby is considerably greater with medical therapy.

PRENATAL CARE

Prenatal care means considerably more than an occasional visit to a physician. There are many grades of care and only a small minority of patients receive adequate care. Grade 1 (a) as described in "Standards of Prenatal Care" (Children's Bureau Publication No. 153) is the desired type to give: This is described as follows:

"1. A careful history, medical, surgical, gynecologic, and obstetric; (2) a complete physical examination, including the examination of heart, lungs, and abdomen; (3) pelvic measurements, both internal and external; (4) the taking of blood for a Wassermann reaction; (5) minute instructions in the hygiene of pregnancy; and (6) visits to a physician at least once a month during the first six months, then oftener as indicated. The first visit must take place not later than the end of the second month. At each of the visits the patient's general condition is to be investigated: blood pressure, urinalysis, pulse, and temperature recorded; weight of the patient taken if possible; abdominal examination made, and the height of the fundus determined."

It was impossible in this series to determine the grade of prenatal care each patient received. One hundred and sixty-one or 54 per cent received no care whatsoever. The remaining 46 per cent made one or more visits to a physician. The care of the latter was far from adequate as determined in a detailed study of 50 of these 299 cases of eclampsia. Of this number only 5 patients received adequate prenatal care as prescribed above. Of the 128 patients noted as having received prenatal care, 8 died, giving a mortality of 0.7 per cent in contrast to a mortality of 33 per cent for those that received no prenatal care.

SUMMARY AND CONCLUSIONS

1. A general statistical study of eclampsia for a five-year period in the State of Maryland has been made.
2. A comparative table of eclampsia in various clinics and countries has been presented.
3. The incidence of eclampsia in the general population of Maryland is 1 in 490, or 20 per cent in contrast to a previous report of 1 per cent for pregnancies given hospitalization.
4. Eclampsia is five times as prevalent in the primigravidas as in multigravidas.
5. The negro population of Maryland showed an incidence of 1 in 310 or 32 per cent.
6. Eclampsia is two and one-half times more prevalent in multiple pregnancy.

There was a small group of infants who showed no clinical signs of erythroblastosis but whose placentas, on examination, showed an increase in the nucleated red cells in the fetal circulation. These infants have not been included because it was felt that many conditions, i.e., partial asphyxia during birth, could cause a temporary rise in the nucleated red cells. An arbitrary level of 15 per cent, or greater, has been taken as an abnormal increase in nucleated red cells in the newborn. This is well in advance of the levels reported by Lippman,⁶ Wintrobe and Shumacker⁵ and others.

CASE REPORTS

Type: Congenital Hydrops

CASE 1.—Mrs. M. K. (2827.) The mother was a 37-year-old American born, para ii. Her first pregnancy, in 1930, terminated normally except that the child was born by breech mechanism. The child was living and well at the time of this pregnancy. The patient's past history was not essential. She was in excellent health during this pregnancy. The delivery occurred at term, on Nov. 1, 1931, and was normal in every respect. The child was a 2,880 gm. female who never breathed well. In spite of all efforts, the infant died three hours after birth. The mother had a negative blood test for syphilis at this time.

The placenta weighed 1,160 gm. The maternal surface was pale in color, deeply fissured in appearance, firm in consistency, but extremely friable. Microscopically, the syncytial cells were immature in appearance. The Langhans layer was partially retained. The stroma was both hyperplastic and edematous. There were many Hofbauer cells present. The vessels were reduced in number and were filled with nucleated red blood cells, those of the erythroblastic type predominating. There were areas of intracapillary erythropoiesis.*

At autopsy, the body was that of a well-developed white female with generalized edema, most marked on the right side. The skin had a slightly icteric tinge and showed many petechiae. There was slight pulmonary congestion and edema, and moderate ascites. The heart weighed 34 gm. (normal full-term weight, 17 gm.) and showed hypertrophy and dilatation of all chambers. The liver was twice normal size and the spleen was enlarged six times. Both organs showed marked erythropoiesis. In addition, there were erythropoietic foci in the adrenals, thymus, and kidneys. Both grossly and microscopically, the bone marrow was hyperplastic, with many primitive red cells in the trabecular spaces. The mother could not be located on the follow-up in January, 1937.

CASE 2.—Mrs. S. C. (RH 864.) The mother was a 36-year-old white American, para iv. She had had her first children normally in 1926 and 1929, respectively. The third child, delivered by Kerr cesarean section on Dec. 13, 1930, because of dilatation and curettage, perineorrhaphy, suspension, and repair of recti, following her second pregnancy, was jaundiced at birth and died in a few hours with a clinical diagnosis of icterus gravis neonatorum. This was confirmed at autopsy. Her past medical and family histories were noncontributory. Other than the previously mentioned operation, she had always been in good health. There was an interval of two years between the third and fourth pregnancy. Her prenatal course during this pregnancy was uneventful. She was subjected to a repeat classical cesarean section at term on March 10, 1932. The baby was a large, pallid male child with advanced generalized edema. It never breathed properly and died thirty-eight minutes after birth.

The placenta weighed 1,230 gm.

*The remaining placentas in the group are pathologically identical; therefore only the weights will be given.

ERYTHROBLASTOSIS

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ERYTHROBLASTOSIS of the newborn has been considered a rare disease. Isolated cases of hydrops fetalis, icterus gravis neonatorum, and congenital anemia appear frequently in the literature. This impression of rarity is contradicted, however, by Ballantyne¹ who was able to collect 70 cases of hydrops fetalis from the literature prior to 1892. In 1931, Ferguson² added a series of 7 cases with autopsies, including both icterus gravis neonatorum, and congenital hydrops. Similarly, Clifford and Hertig² presented a small series of cases. Diamond, Blackfan, and Baty⁴ contributed a complete review of the literature prior to 1934, and a larger series of cases, including congenital hydrops, icterus gravis, and congenital anemia of the newborn. With the exception of the paper by Clifford and Hertig² there has been no attempt to determine the incidence of the disease in a large obstetric service, nor has the obstetric history of women, following the birth of an erythroblastotic child, been investigated. With these facts in mind an analysis of all cases of erythroblastosis occurring in the Boston Lying-in Hospital since 1931 has been made. In addition, the mothers have been interviewed personally in every case where they could be located, and their child-bearing histories analyzed.

In attempting such an analysis certain arbitrary criteria for the diagnosis and classification of erythroblastosis had to be established. All newborn infants showing edema, either generalized or peripheral, associated with a large liver and spleen, extramedullary erythropoiesis and an increase in the number of circulating nucleated red cells, were classified as having erythroblastosis of the hydrops type. The additional presence of jaundice or anemia did not change the classification of the case. However, an infant either born icteric or becoming so within the first forty-eight hours of life, and possessing an enlarged liver and spleen, and an increase in the circulating nucleated red cells, but at no time showing any edema, was classified as having erythroblastosis of the icterus type. The addition or development of severe anemia did not change the classification. There remained in the group, entitled "erythroblastosis of the anemic type," only those infants having severe congenital anemia, an enlarged liver and spleen, and an increase in nucleated red cells, but never showing either jaundice or edema. All infants showing the presence of infection or any congenital anomaly, either during life or at autopsy, were eliminated. No infants whose mothers had positive blood tests for syphilis⁵ were included.

⁵The Hinton Test is used throughout, unless otherwise specified.

tory was noncontributory except for the fact that her younger brother was born jaundiced. Her past history was noncontributory. She had a slight amount of albumin and slight hypertension during the prenatal period of this pregnancy. Her blood test for syphilis was negative. She went into labor spontaneously six weeks before her expected date of confinement, on Oct. 28, 1932. She was delivered of a stillborn female foetus, breech, weighing 3,810 gm. The child had advanced generalized edema. The mother's convalescence was normal.

The placenta weighed 1,040 gm.

At autopsy, the body was that of a well-developed, white, female infant with advanced generalized edema. There were numerous petechiae in the skin. The viscera had a slightly icteric tint. There were numerous subserosal petechiae. A slight ascites was present. The heart was normal in weight. The liver and spleen weighed 156 gm. and 39 gm., respectively. Microscopically, there were foci of erythropoiesis in the liver, spleen, kidney, duodenum, adrenal, thymus, and lymph nodes.

On follow-up in April, 1937, the mother and children were well. She had had an induced abortion in 1933 and then no further pregnancies. The blood test for syphilis was still negative.

CASE 6.—Mrs. R. C. (5279.) The mother was a 40-year-old, white, para xi, whose first child, born in 1915, died within twenty-four hours after birth of an unknown cause. The second and fourth children, born in 1921 and 1922, respectively, died of pneumonia during the first year. The ninth child, born in 1929, a month premature, died at birth. All the other children had normal births and were living and well at the time of this pregnancy. The patient's past history and family history were noncontributory. Her course during this pregnancy was uneventful. She had a negative blood test for syphilis. She gave birth to a 2,490 gm. stillborn, edematous, female child, the fetal heart having stopped two or three days before birth. The mother's convalescence was uneventful.

The placenta weighed 800 gm.

At autopsy, the body was that of a small female child showing some maceration and advanced generalized edema. There was a large amount of straw-colored fluid in the abdominal cavity. The liver and spleen weighed 121 gm. and 20 gm., respectively. There was slight hypertrophy and dilatation of the heart. It weighed 24 gm. There were petechiae in all the abdominal viscera. Microscopically, there was some maceration in all the organs. There were foci of erythropoiesis in the liver, spleen, kidneys, and thymus. The bone marrow showed considerable erythropoietic activity.

On follow-up, in February, 1937, the patient had died with a questionable diagnosis of tuberculosis two years after the birth of this child. She had had no other pregnancies.

CASE 7.—Mrs. E. M. (2832.) The mother was a 30-year-old, white, American born, para iv. The first three children were born in 1927, 1928, and 1930, respectively. At the time of this pregnancy they were all living and well. Her medical, surgical, and family histories were noncontributory. Her prenatal course during this pregnancy was uneventful. She went into labor spontaneously, at term, on Oct. 4, 1932, and was delivered by low forceps of an edematous, 3,890 gm., white, female infant. The child was covered with golden yellow vernix, and lived only two and one-half hours. The mother's postpartum course was uneventful.

The placenta weighed 1,220 gm.

At autopsy, the body was that of a well-developed, white, female child, showing advanced generalized edema. Both ascites and hydrothorax were present. The liver and spleen weighed approximately 234 gm. and 40 gm., respectively. The heart was twice its normal size. Microscopically there were foci of erythropoiesis in the liver, spleen, kidney, and serosa of the small intestine.

On the follow-up, in February, 1937, the patient was well. She had had a normal pregnancy in 1935 and the child was living and well. Her blood test for syphilis was still negative.

At autopsy there was revealed the body of a well-developed white male infant with advanced generalized edema. There was moderate hydrothorax, hydropericardium, and ascites. The heart weighed 40 gm. and showed hypertrophy and dilatation of all chambers. The liver and spleen weighed 200 gm. and 50 gm., respectively. Microscopically, there were foci of erythropoiesis in the liver, spleen, lungs, pancreas, kidney, prostate, thyroid, and dura of the spinal cord.

On follow-up this patient had had no more children. A blood test for syphilis was not taken.

CASE 3.—Mrs. O. B. (RH 2420.) The mother was a 22-year-old white American born, para ii. The first child, born in 1929, was perfectly normal. The past medical, surgical, and family histories were non-contributory. Her antepartum course during this pregnancy was normal. The mother had a negative blood test for syphilis at this time. She was delivered normally at term, on June 23, 1932, of an edematous, 3,240 gm. male infant, covered with yellow vernix. The child died twenty-two minutes after delivery. The mother had an uneventful convalescence.

The placenta weighed 1,150 gm.

At autopsy the body was that of a well-developed, male child with advanced generalized edema. There were a slight hydrothorax and ascites. The heart weighed 26 gm. The liver and spleen weighed 170 gm. and 24 gm., respectively. Microscopically, there were foci of erythropoiesis in the liver, spleen, kidney, thymus, heart, mesentery, and aortic adventitia. There were petechiae in the brain and epicardium, and an old subcapsular hemorrhage in the spleen. There was an incidental small subarachnoid hemorrhage.

On follow-up, the patient had a subsequent normal child, born three weeks from term, in 1933. The child was living and well at the time of the follow-up examination in April, 1937. The patient had an incomplete abortion and dilatation and curettage in 1935. Her blood test for syphilis was still negative.

CASE 4.—Mrs. A. G. (786.) The mother was a 33-year-old colored para ix. Her first two pregnancies resulted in normal babies. The third and fourth pregnancies were terminated by miscarriages at six weeks. Her fifth and sixth pregnancies, in 1930 and 1931, respectively, resulted in normal children. Neither she nor her husband presented any significant family, medical, or surgical history. Her prenatal course during this pregnancy was entirely normal. Her blood test for syphilis was negative. She was delivered, at term, on Aug. 16, 1932, of a stillborn footling, breech, with a prolapsed cord. The child was an edematous female weighing 2,910 gm.

The placenta weighed 1,140 gm.

At autopsy, the body was that of a well-developed, colored female, showing advanced generalized edema, and many petechiae in the skin. There was moderate ascites and hydropericardium. The heart weighed 25 gm. and showed hypertrophy and dilatation of all chambers. The liver and spleen weighed 109 gm. and 25 gm., respectively. There was, in addition, a tentorial tear with massive intracranial hemorrhage. Microscopically, foci of erythropoiesis were found in the liver, spleen, thymus, retroperitoneal lymph nodes, adrenals, kidneys, and pancreas.

The patient was seen again in February, 1937. She had had an ectopic pregnancy with removal of a tube and ovary in 1934. Then, in 1935, she had a perfectly normal child which was living and well at the time of the follow-up visit. A blood test, taken during this visit, was positive (Hinton test). A check-up showed the Wassermann to be positive also.

CASE 5.—Mrs. E. R. (RH 2616.) The mother was a 32-year-old American, para iv. Her first child, born in 1920, was entirely normal. Following this delivery, she had inversion and perforation of the uterus. This was repaired and she had a moderately stormy convalescence. The second child born in 1930, died at three days of age with jaundice, hepatomegaly, splenomegaly, and foci of erythropoiesis in the liver and spleen. The third child was born at home in 1931. The infant was severely jaundiced at birth, but the mother refused to allow it to be transferred to a hospital. In spite of intense jaundice of long duration, the child did well and was in good health at the time of this pregnancy. The mother's family his-

On follow-up in February, 1937, the mother had had no more pregnancies. The blood test for syphilis was still negative.

CASE 11.—Mrs. P. K. (20651.) The patient was a 27-year-old, white, American born, para iii, who had had two normal pregnancies, one in 1931, and the second in 1934.

She had had a 12-pound tumor removed from the left kidney when she was one month pregnant. Medical and surgical histories were otherwise negative. Six weeks prior to delivery, the patient noticed numbness of the right leg, lasting two weeks. For two weeks prior to delivery she had marked edema of the ankles, legs, and face. She felt fetal movements until ten days prior to admission at which time they stopped. On admission, her blood pressure was 164/102, and she showed a trace of albumin in the urine. The blood test for syphilis was negative. Because of presumable fetal death and rapidly developing toxemia, the membranes were ruptured on Oct. 21, 1936, eight weeks from term. Seven hours later she went into labor and delivered a macerated edematous still-born fetus, weighing 2,355 gm. She had a slight febrile puerperium complicated by a hemorrhagic retinitis.

The placenta weighed 1,790 gm. It showed the characteristic pathologic changes.

An autopsy permission was not obtained.

On follow-up, six months later, the mother was well. The blood test for syphilis was negative.

CASE 12.—Mrs. H. B. (71756.) The mother was a 29-year-old, white, American born, para v. She had had two miscarriages and two normal living children. The fourth child was stillborn. Her family and past histories were noncontributory. Her prenatal course during this pregnancy was normal until two weeks prior to admission when she began to have headaches. She developed a rapidly progressive type of preeclampsia and was admitted as an emergency with edema of the hands, face, and extremities, a blood pressure of 150/90, and a large trace of albumin in the urine. In spite of therapy she became progressively worse. On March 24, 1937, when she was eight weeks from term, a Braxton Hicks version was done and a foot brought down. She was then allowed to go into labor and after thirteen and one-half hours she delivered a stillborn 2,880 gm. female infant with generalized edema. The placenta failed to separate and it was necessary to resort to manual extraction. This was followed by so severe a hemorrhage that a 400 c.c. transfusion was necessary. The patient improved rapidly and was discharged on the seventeenth day. The laboratory test of the blood was negative for syphilis.

The placenta weighed 1,260 gm.

At autopsy, the body was that of a well-developed, female infant with advanced generalized edema. There was no jaundice. There was an advanced hydrothorax and ascites. The heart weighed 8 gm. and showed hypertrophy and dilatation, considering the degree of prematurity. The liver and spleen weighed 90 gm. and 10 gm., respectively. On section there were foci of erythropoiesis in the liver and spleen.

On follow-up, six weeks post partum, the patient was well.

CASE 13.—Mrs. H. W. (14577.) The mother was an American born, white, 39-year-old, para xii. She had had eight previous normal pregnancies in 1914, 1916, 1917, 1918, 1920, 1921, 1925, and 1927. One of twins, born in 1921, died at birth. The ninth child, born in 1929, was stillborn and weighed over 15 pounds. It was said to have had the cord around the neck. The tenth child, stillborn in 1932, according to the mother was both jaundiced and edematous. Her past and family histories were noncontributory. Her prenatal course during the eleventh pregnancy was normal except for the fact that she was markedly overweight. Her weight was 175 pounds. The blood test for syphilis was negative. She was delivered normally, at term, of a nine-pound male infant on Sept. 12, 1934. The child was both edematous and icteric at birth. In spite of transfusions, it lived only forty-eight hours.

CASE 8.—Mrs. M. D. (RH 2777.) The mother was a 25-year-old, white, American born, para ii, whose first child was born in 1933. This child was living and well at the time of this present pregnancy. The mother's past and family histories were noncontributory. The prenatal course during this pregnancy was entirely uneventful. She was delivered normally, at term, on Jan. 27, 1934. The child was a 3,420 gm. male infant covered with yellow vernix and having generalized pitting edema. It was in very poor condition, and in spite of a small transfusion became jaundiced and died eleven hours after birth. The mother's convalescence was uneventful.

The placenta weighed 865 gm.

At autopsy, the body was that of a well-developed, male infant with advanced pitting edema and generalized icterus. There was a slight right hydrothorax and hydropericardium. The heart was enlarged, weighing 32 gm. It showed hypertrophy and dilatation of all chambers. The liver and spleen weighed 193 gm. and 30 gm., respectively. Microscopically there were foci of erythropoiesis in the liver, spleen, and kidneys. There was an incidental left subdural hemorrhage.

On follow-up, in April, 1937, the patient had had an induced abortion in 1935. There had been no further pregnancies. The blood test for syphilis was negative.

CASE 9.—Mrs. E. C. (12938.) The mother was a 37-year-old, white, American born, para iv, whose first three children were living and well at the time of this pregnancy. Her past and family histories were noncontributory. She had an entirely negative prenatal course during this pregnancy. Because of a partial placenta previa, and acute hydramnios, the membranes were ruptured at the eighth month of gestation. There was breech presentation and a foot was easily brought down. The child was stillborn and macerated. It weighed 2,730 gm. The mother's postpartum course was uneventful.

The placenta weighed 990 gm.

At autopsy the body was that of a macerated edematous female fetus, measuring 46 cm. in length. The body cavities all contained free bloody fluid. The heart weighed 23 gm. and showed slight hypertrophy. The liver and spleen weighed 158 gm. and 25 gm., respectively. Unfortunately the tissues were too macerated for microscopic study.

On follow-up, in February, 1937, the patient was well. She had had no further pregnancies. She refused to submit to a blood test.

CASE 10.—Mrs. E. C. (13267.) The patient was a 37-year-old, white, American born, para vii. Her first four children were delivered normally in 1923, 1924, 1927, and 1932, respectively, and were living and well at this pregnancy. The fifth baby, born in 1932, was stillborn, at another hospital. The cause of death was unknown. Medically, her past and family histories were not essential. The sixth child weighed 3,960 gm., and was delivered stillborn in 1934, after a prenatal period complicated by mild toxemia and hydramnios.

The placenta weighed 1,350 gm.

There was no autopsy. The mother's puerperium was uneventful.

The seventh child was born one year later. The prenatal period during this pregnancy was uneventful except for a short fetal systolic murmur heard during the last weeks of pregnancy. The patient was admitted two weeks from term, on Dec. 6, 1935, in labor. She was delivered normally of a large edematous male infant which lived thirty minutes. It was covered with yellow vernix.

The placenta weighed 1,275 gm.

At autopsy, the body was that of a well-developed, white, male infant measuring 50 cm. in length. There was soft pitting edema round the neck, of the extremities, and of the genitalia. The skin was slightly icteric, and there were a few ecchymotic areas. There was moderate ascites. The heart weighed (estimated) 40 gm. and showed hypertrophy and dilatation of all chambers. Both splenomegaly and hepatomegaly were present, these organs weighing 120 and 190 gm., respectively. There were petechiae in the skin, thymus, and renal cortex. Microscopically, there was erythropoiesis of the liver, pancreas, kidneys, and adrenals.

The child continued to do well until nine days later, the mother left the hospital against advice, and took the baby with her. The mother had a normal post-partum course except for a thrombophlebitis of the left leg.

On follow-up in April, 1937, the mother and child were well. There had been no further pregnancies.

CASE 3.—Mrs. M. A. (5186.) The mother was a 26-year-old, American born, para iii. Her first two children were born in 1926 and 1929, respectively. Both were living and well at the time of this pregnancy. Her family and past histories were noncontributory. She had an entirely normal prenatal period during this pregnancy. The blood test for syphilis was negative. She went into labor spontaneously on Aug. 19, 1931, and was delivered normally of a 3,570 gm. female infant. The child appeared well but became progressively more jaundiced during the first two days of life. It died suddenly of respiratory failure on the third day after birth. Unfortunately the disease was not recognized clinically and no adequate blood studies were done. The mother's postpartum course was uneventful.

The placenta was not saved for examination.

At autopsy the body was that of a well-developed, white female infant, measuring 35 cm. from vertex to buttocks. There was a deep generalized icterus of the skin but no edema. There was slight hypertrophy and dilatation of the heart. It weighed 25 gm. The other organs were not enlarged. There were petechiae in the epicardium, endocardium, and esophageal mucosa. There was kernicterus of the basal ganglia of the brain. Microscopically, there were foci of erythropoiesis in the liver, spleen, lymph nodes, and adrenals.

On follow-up, in February, 1937, the mother was well. She had had no further pregnancies. She refused to have a blood test for syphilis.

CASE 4.—Mrs. M. G. (RH 1795.) The mother was a 33-year-old, white, American born, para vi, whose first child, born in 1922, was jaundiced at birth and died on the sixth day. The second child, born in 1924, was normal except for a birth palsy. The next three children, born in 1926, 1928, and 1930, respectively, were all deeply jaundiced at birth and died shortly thereafter. She had had an entirely normal prenatal course during all of her pregnancies. Her past and family histories were noncontributory. During this pregnancy she had a large irregular fibroid at the right cornua of the uterus. The prenatal course was uneventful. The blood test for syphilis was negative. She was given a diet, high in nucleoproteins, and rich in liver. She went into labor spontaneously at term, and Nov. 23, 1931, was delivered of a healthy, normal appearing child (male), weighing 3,840 gm. One hour after birth it was noted that there were ecchymoses on the right forearm. The child was immediately transfused with 90 c.c. of maternal blood. The next day the child was jaundiced. The following day the jaundice increased and sixty-five hours after birth the child suddenly became cyanotic and died. The spinal fluid was xanthochromic.

Unfortunately the placenta was not saved for examination.

At autopsy the body was that of a well-developed male infant, measuring 47 cm. in length. There was advanced icterus of the skin and many small subcutaneous hemorrhages. There was no edema and no increase in fluid in the body cavities. The heart was not enlarged. The liver weighed 180 gm. The spleen weighed 28 gm. There was an area of acute infarction of the spleen. There were gross hemorrhages into the adrenal cortex, pleura, pituitary, and epicardium. There was a slight hyperplasia of the bone marrow. Microscopically there were multiple foci of erythropoiesis in the liver, spleen, adrenals, and pituitary. The bone marrow showed advanced erythroblastic activity.

On follow-up, in April, 1937, it was found that the patient had had a hysterectomy in November, 1932. There had been no intervening pregnancies. A blood test for syphilis was not done.

CASE 5.—Mrs. H. J. (6457.) The mother was a 38-year-old, para vi. She had had five children born in 1918, 1922, 1924, and 1928, respectively. The child born in 1922 died at the age of three months of convulsions. All the others were normal.

Unfortunately, the placenta was not saved.

At autopsy, the body was that of a well-developed and well-nourished male infant with advanced icterus and peripheral pitting edema. There was no increased fluid in the body cavities. The heart weighed 36 gm. and showed hypertrophy and dilatation of all chambers. The liver weighed 414 gm. The spleen was also enlarged, weighing 63 gm. The kidneys, too, were increased in size, weighing 22 gm. each (normal, right 14, left 14 gm.). There was kernicterus of the brain. Microscopically, there was erythropoiesis of the spleen, liver, kidneys, and adrenals. Petechiae were present in the epicardium, kidney, adrenal, lungs, and bladder.

The twelfth pregnancy occurred in 1937. She entered the hospital on April 6, 1937, seven weeks from term. She had gained 20 pounds in weight and had had dyspnea and orthopnea for six weeks. The blood pressure was 154/92. She showed a slight trace of albumin. In spite of all therapy and restricted diet, the patient failed to improve. The laboratory test for syphilis in the blood was negative. She went into labor spontaneously on April 12, 1937. During labor she began to bleed profusely. A foot was immediately brought down and a Spanish windlass applied to the mother's abdomen. Two transfusions were given. When the cervix was nearly fully dilated a breech extraction was done and a stillborn, edematous, female infant weighing 3,600 gm. was delivered. The mother did well during her postpartum period except for a day or two of partial anuria immediately following delivery.

The placenta weighed 1,300 gm.

At autopsy, the body was that of a well-developed female, measuring 47 cm. in length. There was generalized edema, most marked over the head, neck, and body. There were many petechiae in the skin over the thorax. There was no jaundice. The abdomen contained approximately 300 c.c. of brownish-yellow clear fluid. The heart showed hypertrophy and dilatation of all chambers. It weighed 30 gm. The liver and spleen weighed 300 gm. and 88 gm., respectively. The bone marrow was hyperplastic. On microscopic section there were foci of erythropoiesis in the liver, spleen, kidney, pancreas, adrenals, and submucosa of the intestine.

Type: Icterus Gravis

CASE 1.—Mrs. S. C. (RH 864.) For case history, see same mother in the preceding group of cases.

The placenta was not saved for examination.

At autopsy, the body was that of a well-developed white female, measuring 54.5 cm. in length, and weighing 3,300 gm. The skin was moderately icteric. There was no edema. There was no excess fluid in any of the body cavities. The heart was normal in size. The liver was not weighed, but was said to be normal in size. The spleen weighed 24 gm. There were petechiae in the brain and viscera. Microscopically the liver, spleen, and kidneys showed many foci of erythropoiesis.

CASE 2.—Mrs. M. O'D. (7302.) The mother was a 32-year-old, white, American born, para iv, whose first child was born in 1919. She had had twins in 1920. These three children were living at the time of this pregnancy. The third pregnancy, terminating in 1922, resulted in an extremely jaundiced infant who died at four days of age. The family history was noncontributory. She had a cholecystectomy in 1930. Her prenatal course during this pregnancy was uneventful. Her blood test for syphilis was negative. She was delivered normally at term after seventeen hours of labor, on Feb. 23, 1931. The child was a normal female weighing 4,230 gm. It became jaundiced within the first day of life. The liver and spleen were enlarged to palpation. The red count was 5.9 million. There were 69,000 nucleated cells, 44 per cent of which were red cells. The icteric index was 300. The child was given a transfusion of 50 c.c. of citrated blood. Two days later the physical findings were unchanged. The red count was 5.9 million. The next day the red count still remained high and there were no nucleated red cells.

ing time normal. In spite of a transfusion of 30 c.c. the child continued to do poorly. The nucleated red cells rose to 80 per cent of the nucleated cells. Jaundice appeared on the second day and the child died shortly thereafter. The mother had an uneventful convalescence.

Autopsy permission was not obtained.

The placenta weighed 570 gm.* It was of normal color and consistency, but the membranes were stained yellow. On section, the villi were slightly larger than normal. The syncytium was slightly immature. The stroma showed slight hyperplasia and edema. The vessels contained many nucleated red cells.

The mother developed mild diabetes during the next pregnancy in 1935. However, under adequate therapy she was delivered of a perfectly normal male infant.

On follow-up in May, 1937, there had been no further pregnancies. The blood test for syphilis was negative.

CASE 8.—Mrs. M. O'B. (10478.) The mother was a 39-year-old, white, American born, para vi. She had five previous normal children, born in 1917, 1921, 1922, 1924, and 1925, respectively. Her family history was noncontributory. Her father died of heart disease. She had had diphtheria at three years of age. Her prenatal course during this pregnancy was normal. She was delivered, at term, on April 8, 1933, of a 4,350 gm. male infant. The child became slightly jaundiced within fourteen hours. The jaundice did not increase, but on April 18, the child became listless and pale and for the first time the spleen became palpable. Blood studies showed hemoglobin 50 per cent, red blood cells 2.5 million, nucleated red cells 10 per cent of the nucleated cells. The child was given a transfusion of 50 c.c. of citrated blood. The red count rose to 3.07 million, and the child was discharged well on April 24, 1933. The mother's post-partum course was uneventful.

The placenta was not saved for examination.

On follow-up in April, 1937, the mother and child were living and well. She had a normal child born in 1935 and following this there were no other pregnancies. The blood test for syphilis was negative.

CASE 9.—Mrs. C. S. (11649.) The mother was a 27-year-old, white, American born, para ii. The first child was delivered by high forceps in 1931. It was living and well at the time of this pregnancy. The mother's past and family histories were noncontributory. Her antenatal course during this pregnancy was uneventful. Her blood test for syphilis was negative. She was delivered at term on Aug. 17, 1933, of a 3,880 gm. male infant. The child appeared normal and cried lustily. However, it was covered with a golden yellow vernix. About eight hours after birth the child developed a deep jaundice and pallor. The liver and spleen were greatly enlarged. Blood studies showed only 1.82 million red cells, 7,800 nucleated cells, 33 per cent of which were red cells. X-ray on the third day showed considerable cardiac enlargement. The child received a total of 18 transfusions at one- to four-day intervals. The nucleated red cells dropped to 11 per cent of the nucleated blood cells within ten days and remained at that level. After five weeks he was transferred to the Children's Hospital. At the time of transfer the red count was only 2 million. He was discharged from there ten weeks after birth with the anemia little alleviated. The mother's post-partum course was uneventful.

The placenta weighed 690 gm.

On follow-up in January, 1937, the mother and both children were well. The mother had had a twenty weeks' miscarriage and no other pregnancies. The blood test for syphilis was still negative.

CASE 10.—Mrs. A. MacD. (15339.) The mother was a 37-year-old, white, American born, para iv, with two living children born in 1927 and 1930, respectively. All her deliveries were by cesarean section, the reasons for which were obscure. In 1933 she had another section, at which time the child was stillborn. The family history was negative. The patient had an appendectomy in 1922. Otherwise her

*The placentas in this group show similar pathologic changes and so only the weights will be given.

The mother's past and family histories were noncontributory. Her prenatal course during the pregnancy was entirely normal. The blood test for syphilis was negative. She entered the hospital two weeks overdue on Jan. 1, 1932, and was delivered normally on the same day of a female child. It was covered with golden yellow vernix. The child never breathed well. It was deeply cyanosed and during the first day both the liver and spleen were felt to be enlarged. The child appeared slightly better the next day, but it was slightly jaundiced. The jaundice deepened on the third day and the temperature rose to 102.6° F. The blood studies showed hemoglobin 96 per cent, red blood cells 3.94 million, white blood cells 34,153. There were 117,500 nucleated red cells and of these 68 per cent were normoblasts, 28 per cent erythroblasts, and 40 per cent myeloblasts. The bleeding time was fifteen minutes. The coagulation time was two to three minutes. A small transfusion was given. In spite of this, the course was progressively downhill. Another transfusion of 40 c.c. was given on the fourth day. Death occurred shortly after this. The mother's post-partum course was uneventful.

The placenta was not saved for examination.

At autopsy the body was that of a well-developed, well-nourished, white female, measuring 44.5 cm. in height. The skin and viscera were deeply jaundiced. There was no edema. The heart was slightly enlarged, weighing 23 gm. There was an early terminal bilateral bronchopneumonia with fibrinous pleurisy. The liver and spleen weighed 220 gm. and 25 gm., respectively. Grossly the bone marrow was hyperplastic. There were petechiae in the pleura, thymus, epicardium, pituitary, brain, kidneys, endometrium, and adrenals. Microscopic examination showed foci of erythropoiesis in the liver, spleen, adrenals, pancreas, and pituitary. The liver showed bile stasis. The bone marrow showed advanced hematopoietic activity with foci of erythroblasts and normoblasts.

On follow-up visit in February, 1937, the mother was living and well. She had had no further pregnancies. She refused to have a blood test for syphilis.

CASE 6.—Mrs. F. P. (9602.) The mother was a 28-year-old, white, American born, para vi. Her first four children, born in 1911, 1913, 1919, and 1923, were living and well at the time of this pregnancy. In 1930 she had an eight-month stillborn child. Between 1923 and 1930 she had married for a second time. Her family and past histories were negative. She had a normal prenatal course during this pregnancy. The blood test for syphilis was negative. She was delivered normally of a 4,230 gm. male infant on Dec. 7, 1932. The child appeared normal but became deeply jaundiced on the day after birth. Both the liver and spleen were enlarged. Blood studies showed 1.9 million red cells, 38,900 nucleated cells, of which 55 per cent were red cells. The patient was transfused immediately and during the next two weeks received 9 transfusions. The red count never rose above 2 million until the last transfusion. The nucleated red cells fell to 10 per cent during the first week. During this time, however, the jaundice deepened and reached an icteric index of 400. At the end of two weeks, nucleated red cells disappeared. The jaundice became less and the red count improved. The child was discharged six weeks after birth. The mother's post-partum course was normal.

The placenta was not saved for examination.

On follow-up in May, 1937, the mother and child were well. There had been no further pregnancies. The blood test for syphilis was refused.

CASE 7.—Mrs. S. L. (RH 2673.) The mother was a white, 38-year-old, American born, para ii. Her first child was normal. Her family and past histories were noncontributory. Her prenatal course during this pregnancy was entirely normal. The laboratory test for syphilis was not done. She was delivered normally of a 3,360 gm. male infant on Dec. 10, 1932. The child was covered with yellow vernix and quite cyanotic at birth. It never breathed well. Petechiae developed over the scalp. The liver and spleen were enlarged to palpation. Examination of the blood showed 4.1 million red cells, 14,000 nucleated cells, 64 per cent of which were red cells. The hemoglobin was 105 per cent. Clotting time was thirty minutes. Bleed-

weighing 3,260 gm. The child appeared normal, but developed jaundice during the second day. The liver and spleen were palpable at this time and blood studies showed 2.5 million red cells, 8,500 nucleated cells, with 50 per cent of these being red cells. The child was immediately transfused. The next day the nucleated red blood cells dropped to 35 per cent of the nucleated cells. Six days later the red cell count was 2.5 million. The child was again transfused and the red count rose to 2.5 million and remained there until discharge twenty days after birth. The mother's convalescence was uneventful.

The placenta weighed 650 gm.

On follow-up in March, 1937, her children were all living and well. The mother had had no further pregnancies and the blood test for syphilis was still negative.

CASE 13.—Mrs. G. F. (16827.) The mother was a 28-year-old, American born, white, para iii whose first child, born in 1932, was living and well at the time of this pregnancy. The second child, born in 1933, one month prematurely, was said by the father to have died of jaundice at three weeks of age. The mother's family and past histories were noncontributory. Her prenatal course was perfectly uneventful except for a slight elevation in blood pressure and slight albuminuria. Her blood test for syphilis was negative. She was delivered normally, at term, on May 19, 1935, of a 3,210 gm. female infant. The child became jaundiced shortly after birth. The liver and spleen were both palpable and moderately enlarged. Blood studies showed 2.21 million red cells and 63,000 nucleated cells, 64 per cent of which were red cells. The child was given an immediate transfusion with 65 c.c. of citrated blood. The next day the red count was 3.4 million. There were 82,000 nucleated cells, 58 per cent of which were red cells. There was rapid improvement and the patient was discharged well on the fourteenth day. The mother's postpartum course was uneventful.

The placenta weighed 460 gm.

On follow-up in April, 1937, the mother and child were well. There had been no further pregnancies. The blood test for syphilis was still negative.

CASE 14.—Mrs. J. R. (5113.) The mother was a 43-year-old, Irish born, para v. Her children were born in 1918, 1921, and 1930, respectively. They were normal. The fourth child, born in 1931, died of an intracranial hemorrhage. Her family history was noncontributory. She had been a known diabetic for two years preceding this pregnancy. Her blood test for syphilis was negative. However, subsequent examination showed the husband to have a positive blood test for syphilis. She gave birth to a jaundiced 5,130 gm. female infant on Aug. 1, 1935. The child's face was covered with petechiae. The spleen and liver were both enlarged. The blood studies showed 4.3 million red cells, 55,000 nucleated cells, 80 per cent of which were red cells. She was given a transfusion of 45 c.c. of citrated blood. The next day the child showed typical signs of intracranial hemorrhage. Four days later she became severely jaundiced. The red count dropped to 3.2 million. The nucleated cells numbered only 9,000 and the red cells included only 14 per cent. The liver and spleen were noticeably increased in size. Because of a severe anemia she was transfused on the eleventh day and parental fluids were given at intervals. She was transfused again on the thirteenth, fifteenth, seventeenth, twenty-fifth, and thirty-fourth days. After this the blood tended to remain around 3.5 million. The jaundice had disappeared with the onset of the anemia on about the thirteenth day. The child's blood test for syphilis was negative. The child was discharged on the fifty-third day. The mother's post-partum course was uneventful, except for a few insulin reactions.

The placenta was not saved for examination.

On follow-up in April, 1937, the patient had had no further pregnancies. The condition of both mother and baby was good.

CASE 15.—Mrs. A. F. (8844.) The mother was a 23-year-old, white, American born, para iii. Her first child, born in 1932, was living and well at the time of this pregnancy. Her second pregnancy resulted in a stillborn infant. Her family history was negative. She had had whooping cough, and a tonsillectomy and

past history was not unusual. Her prenatal course during this pregnancy was not remarkable, except for the fact that she showed a slight trace of albumin just before entering the hospital. The blood test for syphilis was negative. A repeated classical cesarean section was done three weeks before term, on Dec. 22, 1934. At this time the mother was sterilized by the Irving technique. The child weighed 3,315 gm. and was to all appearances normal. However, it became jaundiced three hours after birth. The liver and spleen were clinically enlarged, and blood studies showed the hemoglobin to be 100 per cent, red blood cells 4.8 million, nucleated cells 62,000, with 80 to 85 per cent of these red blood cells. Most of the nucleated red cells were erythroblasts. A transfusion of 45 c.c. was immediately given. The following day the jaundice increased rapidly and the red count dropped to 2.8 million. The child developed a severe epistaxis, on the third day, and this could not be stopped. In spite of another transfusion, death occurred thirty hours after birth. The mother's convalescence was uneventful.

At autopsy the body was that of a well-developed, white, male infant, measuring 50 cm. in length. The skin and scleras were diffusely icteric, having a peculiar orange-yellow color. The peritoneal cavity contained a small amount of dark fluid. There was no increase of fluid in any of the other body cavities. The heart weighed 26 gm. and showed slight hypertrophy and dilatation of all chambers. The liver and spleen weighed 174 gm. and 44 gm., respectively. Grossly, the brain showed kernicterus of the basal nuclei. There were petechiae in the lungs, spleen, pericardium, bladder, and pleura. The bone marrow was not hyperplastic. Microscopically there were multiple foci of erythropoiesis in the liver, spleen, kidney, and pancreas. There was slight hyperplasia of the bone marrow with islands of erythroblasts.

The placenta was not saved for examination.

On follow-up examination in March, 1937, the mother was well. There had been no further pregnancies. The blood test for syphilis was not done.

CASE 11.—Mrs. N. H. (13929.) The mother was a 32-year-old, white, American born, para iii. Her first two children were normal in every respect. Her family and past histories were noncontributory. Her prenatal course during this pregnancy was normal. The blood test for syphilis was negative. She was delivered normally, at term, on March 14, 1937, of a 3,090 gm. jaundiced male infant. Both the liver and spleen were slightly enlarged. Blood studies showed 6 million red cells, 48,000 nucleated cells of which 26 per cent were red cells. The following day the red count fell to 5.1 million and the nucleated cells were 36,700. Ninety-seven per cent of these were red cells. The child was given transfusions on the second, third, and fifth days. The red count remained at 4 million until the eighth day when it fell to 1.5 million. The child was again transfused on the eighth and tenth days. The red count then remained above 4 million. The nucleated red cells disappeared from the blood stream on the fifteenth day. The jaundice gradually disappeared during the third week. The child was discharged five weeks after birth. However, it never developed normally and has had to remain in an institution. The mother's convalescence was normal.

The placenta was normal grossly. It was not saved for microscopic examination.

When seen in April, 1937, the mother was again pregnant. The blood test for syphilis was still negative.

CASE 12.—Mrs. D. B. (16449.) The mother was a white, 39-year-old, American born, para v. Her children, born in 1924, 1926, 1929, and 1931, were all living and well at the time of this pregnancy. The mother's family history was noncontributory. She had had her tonsils and adenoids removed in childhood. She stated that she had had an embolism following the birth of her fourth child. She had a very slight degree of hypertension during the last part of this prenatal period. Her blood test was negative for syphilis and otherwise her course during this pregnancy was normal. She was delivered normally at term, on April 5, 1935, of a male infant

living and well at the time of this pregnancy. The third child, born in 1932, died of "jaundice" at four days of age. The family and past histories were non-contributory. She had a normal prenatal course during this pregnancy. The blood test for syphilis was negative. She was delivered, at term, on Sept. 17, 1936, of a 3,660 gm. male infant. The child became jaundiced soon after birth. The jaundice deepened, but it was not until the child became very pale and apathetic on the eighth day, that any alarm was felt. Blood studies then showed 1.86 million red cells. There were only two nucleated red cells per 100 nucleated cells. The child was given a 75 c.c. transfusion. The red cells promptly rose to 4.98 million. Two days later the red count had again fallen to 2.9 million and the nucleated red cells made up 10 per cent of the nucleated cells. Another transfusion was given and the red count rose to over 4 million where it remained in spite of a mild omphalitis occurring during the third week. The child was discharged five weeks after birth. The mother's post-partum course was normal. The placenta was not saved.

On follow-up in April, 1937, the mother and baby were living and well. There have been no further pregnancies. The blood test for syphilis was negative.

CASE 19.—Mrs. E. N. (5435.) The mother was a 27-year-old, Italian, para iv. Her first child, born in 1931, had a normal delivery and was living and well at the time of this pregnancy. Her past and family histories were noncontributory. She had a functional systolic murmur during the second pregnancy. Otherwise her antenatal course was entirely normal. Her blood test for syphilis at this time and on her first visit was negative.

She was delivered normally at term on Dec. 10, 1931, by low forceps. The child was a male and weighed 3,090 gm. The infant was covered with golden yellow vernix. It developed a deep jaundice during the first day of life. The heart was not enlarged but the liver and spleen were easily palpable. Blood studies showed 3.1 million red blood cells, 85 per cent hemoglobin, and 40,900 nucleated cells. There were 17.5 per cent of the red cells reticulated and 21.0 were nucleated. The bleeding and clotting time was normal. The patient was given a 60 c.c. transfusion. During the stay in the hospital it received five additional transfusions, and some intramuscular liver. The jaundice deepened and on December 29, it reached an icteric index of 325. The red count was 4.12 million eight days after birth. From this point on there was a fall on two occasions to 2.47 and 2.61 million, respectively. These periods of severe anemia were counteracted with transfusions. The nucleated red cells disappeared from the blood stream on the seventh day. The child was discharged on Feb. 1, 1932, with a slight persistent anemia. The icteric index had fallen to 75 at the time of discharge. The mother had a slightly febrile puerperium.

The placenta weighed 810 gm.

On Oct. 17, 1935, the patient was delivered normally, at another hospital, at term, of a normal appearing female child. The mother's prenatal course, according to her, was perfectly normal. The child became jaundiced during the first few hours of life. In spite of the mother's statement to the attending physician regarding a history of erythroblastosis, the child received no treatment. It died suddenly on the eighth day. The mother's postpartum course was uneventful.

On March 12, 1937, after a perfectly normal prenatal course, the mother was delivered normally of a 3,570 gm. male infant. Smear of the cord blood showed 17 per cent nucleated red blood cells. The baby became jaundiced after six hours. Blood studies at this time showed 5.4 million red cells, hemoglobin 100 per cent, nucleated cells 20,000, of which 2 per cent were red cells. The bleeding and clotting times were normal. The red cells had a slightly increased resistance to hypotonic saline. At the end of twenty-four hours, the spleen and liver were definitely enlarged. The jaundice deepened rapidly, and the skin became olive green in color. The patient was given a 50 c.c. transfusion on March 13, 1937. The next day there were no nucleated red blood cells. The jaundice disappeared on

adenoidectomy in childhood. Her prenatal course during this pregnancy was normal. Her blood test for syphilis was negative. She was delivered by low forceps, at term, on December 5, 1935. The child, a male, weighed 3,750 gm. and was jaundiced at birth. On physical examination, the liver and spleen were enlarged and blood studies showed 2.8 million red cells and 31,000 nucleated cells of which 76 per cent were red cells. The child was immediately given a transfusion of 80 c.c. of citrated blood. The red count rose to 3.8 million. He was transfused again on the third, seventh, eleventh, thirteenth, and forty-third hospital days. On discharge, the red count was 3.8 million and none of the red cells were nucleated. The mother's post-partum course was normal. The placenta weighed 735 gm.

On follow-up in February, 1937, the child and mother were well. She had had no further pregnancies and her blood test for syphilis was still negative.

CASE 16.—Mrs. G. B. (19067.) The patient was a 21-year-old, white, American born, para ii. She had one previous child, born in 1933, who was living and well at the time of this pregnancy. Her family history was noncontributory. She had had purpura hemorrhagica during childhood. In 1922 she had a tonsillectomy and adenoidectomy. In other respects her past history was not essential. Her antenatal course during this pregnancy was entirely normal. Her blood test for syphilis was negative. She was delivered at term on Jan. 31, 1936, in the outpatient department. The child, a male, weighed 3,720 gm., and was apparently in good health. It developed jaundice during the first twelve hours. This became progressively worse during the next five days. A smear was reported negative for erythroblasts by the externe. The child died suddenly on the sixth day. The mother's post-partum course was uneventful.

The placenta was not saved for examination.

At autopsy, the body was that of a well-developed male infant, measuring 50 cm. in length. There was a deep icterus of the skin and viscera. There was no edema and no increase of fluid in the body cavities. The heart weighed 21 gm. The liver and spleen weighed 134 gm. and 30 gm., respectively. There was kernicterus of the basal nuclei of the brain. On microscopic examination there were many foci of erythropoiesis in the liver, spleen, and pancreas. The vertebral bone marrow showed advanced erythroblastic activity.

The follow-up examination in March, 1937, showed the mother to be pregnant again. The blood test for syphilis was still negative.

CASE 17.—Mrs. N. J. (19742.) The mother was a 30-year-old, white, Irish born, para iv. Her three previous children were born in 1932, 1933, and 1934, respectively. The first two were normal. The third was born jaundiced and did poorly during its early life. They were all living and well at the present pregnancy. Her family history was noncontributory. She had a vaginal repair and appendectomy in 1936. Her prenatal course during this pregnancy was uneventful. Her blood test for syphilis was negative. She was delivered normally, at term, on July 1, 1936, of a 2,865 gm. male infant. The child was in good condition but pale in color and slightly jaundiced. The liver and spleen were not felt. Blood studies showed the hemoglobin to be 64 per cent, red blood cells 2.4 million, nucleated cells 35,600, of these 26 per cent were red cells. The child was immediately transfused with 50 c.c. of the mother's blood. The next day the liver and spleen were palpable but the red cell count had risen to over 5 million. Three days later the jaundice had disappeared. The liver and spleen were not palpable and the nucleated red cell count had dropped to 10 per cent of the nucleated cells. A week later the red count dropped to 3.07 million and the child received a 45 c.c. transfusion. It was discharged two days later. The mother's puerperium was uneventful.

The placenta was not saved for examination.

On follow-up in April, 1937, the mother and baby were well. She had had a ten-weeks miscarriage in March, 1937. The blood test for syphilis was still negative.

CASE 18.—Mrs. D. C. (69750.) The mother was a 28-year-old, American born, white, para iv. Her first two children, born in 1926 and 1931, respectively, were

The heart, liver, and spleen were enlarged and extramedullary erythropoiesis was found in the liver and spleen without exception and frequently in other organs.

There are 11 females in which the disease was present first in the hydrops variety. The average maternal age is 31.6 years and the average parity is 5.2. This confirms the opinion that erythroblastosis is a disease of the middle or late child-bearing period and occurs only with the greatest infrequency in primiparas. This disease occurred in consecutive siblings in 2 of the 11 families listed, and showed, in the remainder, a definite tendency to be the final episode in the child-bearing histories of these mothers. Before the occurrence of erythroblastosis in these families there were 31 normal infants and 9 stillbirths. Following the birth of the erythroblastic infant there were three normal children, three stillbirths, three infants with congenital hydrops and none with icterus gravis. In this group, therefore, the chance of having a second infant suffering from congenital hydrops is 50 per cent.

DISCUSSION: ICTERUS GRAVIS

There were 20 infants with icterus gravis born to 19 mothers during the period under consideration. The incidence is thus approximately one in 1,500 deliveries. The infants in this group were normal in weight and showed approximately equal sex distribution. Only a few of the placentas were saved for examination, but these showed a normal gross appearance and were of normal weight. It was only on microscopic examination that changes consistent with the diagnosis of erythroblastosis could be made out. The presence of yellow vernix was again of no diagnostic importance. However, anemia was present to some degree in 80 per cent of the infants. In most instances the anemia appeared late, after the disappearance of the jaundice and the circulating nucleated red cells. It is this fact and the failure to find any cases which satisfy the original criteria for the diagnosis of congenital anemia which lead, inevitably, to the conclusion that the so-called congenital anemia of erythroblastosis is not an entity but a sequel to icterus-gravis. That the jaundice and increase in circulating nucleated red cells may be a very transient condition is well demonstrated in some of these infants. The infant mortality in this group was 53.8 per cent. It is evident that those infants who died were either not transfused or the transfusions were inadequate and were given too late. The entire group showed enlargement of the liver and spleen and occasionally the heart. This was also evident in the 6 post mortem examinations. Extramedullary erythropoiesis was present as in the previous group but to a less marked degree. The average age of the mothers is 30.1 years and the average parity 3.4. There was one primipara in this group. There were 44 normal infants and 6 stillbirths prior to the birth of the icteric infant. Following this there were 3 normal infants, 3 stillbirths, 1 child with congenital hydrops, and 12 with icterus gravis. The disease showed a familiar incidence in seven of the twenty

March 17, 1937, and with this there was a progressive fall in the red count. When this reached 2.3 million, a 60 c.c. transfusion was given. The next day the red count was 2.18 million and a transfusion of 120 c.c. of blood was given. Following this transfusion there was a progressive rise in the red count to 4.75 million. The red count then fluctuated between 4.70 million and 4.03 million at discharge. The mother's postpartum course was uneventful.

The placenta weighed 540 gm.

The patient and child were living six weeks following discharge. The child was still quite anemic and was receiving treatment at the Boston City Hospital. The blood test for syphilis was not taken.

DISCUSSION: CONGENITAL HYDROPS

At first glance it would seem futile to derive statistical data from such a small series of cases. However, inasmuch as no similar series appears in the literature, it was felt that any data so derived would at least serve the purpose of indicating a trend.

Since 1930 there were 15 infants suffering from congenital hydrops born to 13 mothers in the Boston Lying-in Hospital. During the same period there were 30,299 deliveries. The incidence of congenital hydrops in this series is, therefore, approximately one in every 2,000 deliveries. Little pertinent information can be gained either on questioning the mothers or on examination of the records regarding the prenatal period. Toxemia in some degree occurred in 30 per cent of the cases or an increase of five times the incidence in the clinic. While this is of interest and has been noted by many of the German authors, it is felt that toxemia is rather an indication of a disturbed maternal metabolism and not an etiologic factor. Contrary to the prevailing opinion that the hydrops infants are heavier than normal, these infants average 6.6 gm. under the normal average given by (Riggs¹). There is some error in this average due to failure to correct for prematurity in a few of the cases. This correction, however, is insignificant. The placentas average 1183.5 grams in weight and give a fetal placental ratio of 3 to 1 instead of the normal of 6 to 1. All the placentas present a typical pathologic picture. Sex played no factor in the series. Yellow vernix first described by DeLange and Artzenius³ and later emphasized by Clifford and Hertig² as a diagnostic aid occurred only three times. It is seen so often in infants exhibiting fetal distress during the second stage of labor that it can be considered of negligible diagnostic importance. Icterus occurred in 30 per cent of the cases. This is one of the factors that helps to emphasize the close relationship between congenital hydrops and icterus gravis. The infant mortality in congenital hydrops is 100 per cent. The infants are either stillborn or live only a few minutes though one infant survived forty-eight hours. Autopsies were performed on all but two of the infants. Because of inadequate history and lack of post mortem examination, E. C. 13,627 (first erythroblastotic infant) did not conform to the criteria for diagnosis. However, the gross and microscopic picture of the placenta and the appearance of the disease in the subsequent child leaves little doubt as to the validity of the diagnosis. The autopsy findings were consistent throughout. All but one infant showed an increase in the fluids of the body cavities.

PUERPERAL GANGRENE OF THE EXTREMITIES

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FORTUNATELY, post-partal and post-abortion gangrene of the extremities, with its very serious prognosis, is an extremely infrequent complication. In 1932, McNally collected 99 cases from the literature. To this series he added a case of his own, gangrene following a cesarean section. He reviewed the entire group, finding 72 cases of post-partal gangrene of the lower extremities, 12 cases of post-abortion gangrene of the lower extremities, 11 cases of post-partal gangrene of the upper extremities, 1 case of post-abortion gangrene of the upper extremities, and 4 instances in which gangrene occurred during pregnancy. Unquestionably, several of the cases included in the series are of doubtful authenticity, since it includes women who developed gangrene more than one month after labor, patients who had received ergot or one of its derivatives, and likewise, women in whom other basic maladies such as Raynaud's disease or toxemic states, such as eclampsia, existed.

Subsequent to McNally's report, Cutchin's case is the only one published in English. In 1934 he reported a multipara who had received 4 drams of ergot over a period of two days because of continuous and severe bleeding. Dry gangrene of both legs was definitely apparent by the twelfth day, at which time she died of pneumonia. In this case too, the significance of the ergot ingested must be evaluated.

The following case is of particular interest because of the minimal indications of infection preceding the onset of the gangrene, and because no other factors such as ergotism, excessive hemorrhage, or coincidental diseases need be considered.

L. M., a twenty-year-old white woman, married sixteen months, gravida i and para i, was admitted to City Hospital on Jan. 2, 1935, with the history of having been delivered at home with forceps on Dec. 17, 1934. Subsequent to delivery, there occurred a profuse, foul vaginal discharge. There were neither chills nor fever. She remained in bed after her delivery until she sought admission to the hospital because of pain and tenderness in her left leg.

Examination showed her general condition to be excellent. She was moderately obese. Tenderness and spasm were elicited in both lower abdominal quadrants. The uterus could be palpated 3 cm. above the symphysis. Exquisite tenderness of the left calf with glistening tenseness of the skin was noted. There was no evidence of venous pathology. The left foot was normal.

Two days after admission, the tenderness and swelling of the left calf had increased markedly and saphenous vein tenderness was evident. At this time, her temperature was 101° F. By January 5, the patient appeared quite ill, and had severe pain in both lower extremities. There was marked edema of both thighs, legs, and feet. Both feet were cool and livid. At this time, her temperature had dropped to normal levels.

On January 7, bleb formation was noted on the left leg, suggesting a burn. One week later, a large bleb on her right foot was aspirated, yielding 20 c.c. of straw-colored fluid which cultured negatively. On January 17, dry gangrene of the distal parts of the soles of the feet and the toes was definite. Both lower extremities were tensely swollen, although there was no pitting edema at any time. The tenderness gradually grew less. On this same date, the picture was complicated by infarction of the right lung base. Respiratory symptoms and elevated temperature were evident until January 29. On January 30, superficial gangrene of the left ankle was noted. At this time morphine gave very little relief of pain.

Disproportion between the temperature (98.4° F.) and the pulse (130) was first noted on February 13. At about this time, the lines of demarcation were gradually

families considered. The chance of a subsequent infant suffering from erythroblastosis in this group is 80.3 per cent.

Because of the familial characteristic of the disease one family in each group was carefully investigated for 4 generations. There is no evidence that the disease has any congenital characteristics.

The similarity of the placentas of infants suffering from congenital hydrops to those described as occurring in infants with congenital syphilis led to a careful investigation of this aspect. The blood tests of all the mothers were negative either at the time of delivery, or at the follow up visit, during this investigation, or both. One mother, A. G., had a positive blood test at follow up visit but she showed no evidence of syphilis at the time of the birth of her child. At post mortem examination of the infants in the hydrops group the livers were stained according to the Levaditi method but no spirochetes were found.

CONCLUSIONS

1. Fifteen infants suffering from congenital hydrops and twenty suffering from icterus gravis are presented.

2. This represents an incidence of 1 in 2,000 deliveries in the first group and 1 in 1,500 deliveries in the second.

3. The infant mortality is 100 per cent in the first group and 50.3 per cent in the second.

4. The importance of the early diagnosis of icterus gravis and of early and adequate transfusion is emphasized.

5. Early diagnosis can only be accomplished with accuracy by careful placental studies and examination of the cord and infant blood in all suspected cases.

6. The incidence of recurrence of the disease in subsequent infants in the same family is 50 per cent in the first group and 80.3 per cent in the second.

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Schleyer, E.: New Symptom for Differentiation of Inflammatory and Noninflammatory Genital Tumors. Zentralbl. f. Gynäk. 61: 1176, 1937.

Schleyer describes the value of rectoscopic examination in differentiation of inflammatory and noninflammatory genital tumors. He found that, if rectoscopy reveals proctosigmoiditis or sigmoiditis, the tumor of the genital adnexa generally is inflammatory, whereas normal mucosa in the sigmoid indicates a noninflammatory genital tumor.

J. P. GREENHILL.

TRUE KNOT OF UMBILICAL CORD CAUSING FETAL DEATH BEFORE LABOR

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S. M., a 29-year-old, para 3-0-0-3,* was admitted to the University Hospital at term and in labor. Her family history included the history of one sibling stillborn, and the patient herself was born with a congenital absence of the left arm below the elbow joint.

Her prenatal course also had been characterized by a slight elevation of blood pressure which, however, was easily controlled by diet and purgation. The past obstetric history was entirely normal.

Admission examination revealed a term pregnancy, R.O.A., but persistent efforts to locate the fetal heart were unsuccessful and, upon questioning the patient, it was learned that there had occurred a complete and abrupt cessation of fetal movements seventy-two hours prior to the onset of labor which was preceded by a period of unusual fetal activity lasting approximately twenty-minutes.

Her labor was of normal progression and rectal examinations throughout gave the impression of a boggy presenting part instead of the usual firm sensation of the fetal skull bones. After nine hours she was delivered spontaneously of a full-term dead male child weighing 7 pounds 2 ounces.

There was a true knot of the umbilical cord 45 cm. from the placenta and 17 cm. from the child. Circulation was completely obliterated and the cord between the knot and the baby was enlarged, spongy, friable and darkened to a brownish-gray hue. The fetus was macerated and the cranial bones were overlapping. An autopsy was unobtainable.

Her puerperium was complicated by a mild puerperal infection lasting two days. She responded readily to treatment and after eleven days of hospitalization was discharged in good condition.

COMMENT

This case is an exception to the popular belief that knots drawn tightly enough to cause fetal death occur only during labor. The sudden extreme fetal activity preceding complete absence of movements is significant and is sufficient to make the diagnosis where no other pathology can be found. If the knot is tightened only during labor, the cause of fetal death in utero is more likely to be attributed to some other cause until delivery is effected. It follows, therefore, that careful inspection of the cord should be a matter of routine in all cases of stillborn infants.

I wish to thank Dr. L. H. Douglass of the Department of Obstetrics for permission to use this case.

*The first figure represents the number of full-term children whether alive or stillborn; the second, the number of prematures; the third, the number of abortions (before the twenty-eighth week); and the fourth shows the number of living children.

deepening to the bone. On February 18, the right foot was amputated through the line of demarcation (through the tibio-astragaloid joint). On March 1, the left foot was amputated through the line of demarcation (including the lower two inches of the tibia and fibula). Up to March 15, the patient was more comfortable, and the stumps remained clean. During this period, opiates afforded relief. On March 20, she developed a large decubitus ulcer of the back. From March 25 to 30, the patient was intermittently delirious. She was discharged, upon her insistence, in a slightly improved condition, on April 6, 1935. Several blood transfusions had been



Fig. 1.—Appearance of feet on Jan. 17, 1935, one month after delivery. Dry gangrene is bilaterally evident, and the lines of demarcation are beginning to appear.

given during her stay at the hospital and repeated blood cultures had been negative. During the first two months of hospitalization, her temperature curve had swung between 100° and 103° F. Later it remained lower.

She was readmitted on April 22, and on April 25 was transferred to Bellevue Hospital (Psychiatric Division) where she died of sepsis on May 10, 1935.

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Mayor, J. M.: *The Inhibitory Action of Follicular Hormone on Milk Secretion in the Puerperium.* *Zentralbl. f. Gynäk.* 60: 2379, 1936.

Mayor describes the results of treatment of 47 women who had been delivered recently and in whom lactation was not to be established. The cases included deliveries at term, premature deliveries and abortions. A hormonal injection was made during the first twenty-four hours after delivery and then once daily, the injection being intramuscular in each case: 14 patients were given menformon and the rest progynon B oleosum.

The author concludes: (1) intramuscular injections of follicular hormone undoubtedly have an inhibitory effect on mammary secretion. (2) Daily doses of 200 to 10,000 mouse units of follicular hormone, six to eight days after each other, produce no clinically valuable result. (3) Doses of 250,000 mouse units of follicular hormone in one injection yield a valuable clinical result. (4) The exact boundaries of the indications for such treatment will have to be worked out after further experience. The author suggests the use of follicular hormone in all cases of dead fetus or abortion.

definite line of demarcation appeared and amputation was done in the middle third of the leg on November 14. Convalescence was smooth and she was able to leave the hospital Nov. 25, 1932.

CASE 3.—Mrs. S. L. M., aged 30, para iii, was admitted to the hospital April 24, 1933, complaining of fever, chills, loss of weight and strength. She complained also of pain in the fingers, left elbow and hip and right knee. The onset of illness was three months before admission, beginning with vaginal bleeding; shortly thereafter the vaginal discharge became foul and profuse. Abortion was denied but she admitted amenorrhea of two months before onset of present illness. She looked gravely ill. The temperature was 103° F., and the pulse 130. There was limitation of motion and tenderness of the left elbow and right knee; the knee was slightly swollen. There was a foul vaginal discharge; the uterus felt a third larger than normal and was fixed in moderate retrodisplacement. Pelvic tenderness was definite but not pronounced and no adnexal or parametrial masses were felt. The blood culture yielded a nonhemolytic streptococcus.

Treatment consisted of supportive measures together with repeated small blood transfusions. On May 3 the right knee became more painful and the swelling increased. Bluish red spots were noted over the foot May 5; this discoloration increased and extended up the leg, which became cold and cyanotic. By May 8 the leg was definitely gangrenous and the patient appeared in extremis; however, she improved slightly following transfusion and amputation was done in the middle third of the thigh May 9. Only temporary improvement followed operation, the patient dying May 28, 1933.

Examination of the amputated extremity showed thrombosis of all the veins; the arteries were grossly normal.

Postmortem Findings.—The uterus was approximately a fourth larger than normal and bound to the posterior pelvic wall by adhesions. In the uterine cavity was found a mass of tissue measuring 3 by 3 by 2 cm.; it was firmly adherent to the uterine wall and was grossly a piece of placental tissue. The pathologist reported, "Sections of this tissue showed many decidual cells and degenerated tissue together with inflammation." The common, external and internal iliac veins were filled with thrombi. Each femoral vein contained a semisolid purulent material. The left pampiniform plexus was thrombosed as was the inferior vena cava in its first two inches. The abdominal aorta, the common, external and internal iliac and femoral arteries were grossly normal.

Similar in many respects to the preceding cases, yet differing in that gangrene did not occur, was the case of Mrs. A. M., aged 24, para iv, who was seen during February, 1937. She had been delivered by a midwife eleven days earlier. She complained of severe pain in the right foot and leg. The foot and lower half of the leg were cold, cyanotic, tender, and swollen. The foot and toes could be moved; however, tactile sensation was lost over the lower third of the leg and the foot, and deep sensation of the toes was lost. Femoral and popliteal pulsations were felt and it was thought the dorsalis pedis could be felt to pulsate. The treatment was heat, elevation, and medication for the relief of pain. Recovery took place instead of the expected gangrene. In the foregoing cases coldness, cyanosis and loss of sensation had presaged loss of the extremity. It seems logical to presume that all the veins were not thrombosed in this case, enough being patent for the establishment of collateral circulation.

SUMMARY

1. Four cases of puerperal thrombophlebitis are presented, three of which developed gangrene.

2. While rare, gangrene of an extremity may occur from the venous obstruction of puerperal thrombophlebitis when the thrombosis is unusually extensive.

3. Venous thrombosis of the puerperium is on an infectious basis. Case 3 illustrates the danger of leaving a fragment of placenta in the uterine cavity, which can usually be safely removed at the time of delivery if the principles of asepsis are respected.

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GANGRENE OF THE EXTREMITIES IN PUERPERAL THROMBOPHLEBITIS

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THAT puerperal gangrene is of rare occurrence is attested by the small number of cases recorded; reports in the literature indicate 105 to April, 1937. Infection is the common etiologic factor, with arterial obstruction mentioned as the direct cause of gangrene in most of the reported cases.

As is well known extensive thrombosis may occur in thrombophlebitis, complicating the puerperium, and the tense swollen leg show no signs of venous congestion. It is believed that this swelling may be due largely to lymphatic obstruction. The femoral vein in man may be ligated with only evanescent venous congestion and ligation of the femoral vein in dogs is followed by no congestion whatever (Homans¹). The absence of venous congestion is explained by the ease with which venous blood finds its way past an obstruction, there being abundant pathways for the establishment of collateral circulation. Despite these facts gangrene may result from venous obstruction, as demonstrated by the cases I wish to report.

During a period of eighteen months three cases of puerperal thrombophlebitis which developed gangrene were seen at the Lawrenceburg Hospital, two following full term delivery and one following abortion. These patients, so far as could be determined, had no preexisting cardiovascular disease or other disease which might predispose to gangrene. Ergot had been administered to each of them before admission to the hospital, but the symptoms and physical signs did not suggest ergot poisoning. Three amputations were done, with the usual clinical criteria for determining the level of amputation being observed. In one case there was a definite line of demarcation. Femoral pulsation was felt in each case and arterial patency at the site of amputation was demonstrated by allowing momentary spurting. Careful dissection of the amputated extremities revealed obstruction of all the veins; the arteries were grossly normal and no obstruction could be demonstrated.

CASE 1.—Mrs. D. S. B., aged forty-four, para viii. There was nothing remarkable in her previous obstetric history. She was delivered of a 10-pound infant on Nov. 13, 1931, at full term and without difficulty. The attending physician had not seen her before the onset of labor but found the temperature, blood pressure, and urine normal. The pulse at the time of delivery was 120 and was found to be rapid at subsequent observations during the puerperium, this being suggestive of thrombophlebitis. Otherwise the puerperium was not remarkable until fourteen days after delivery when she began to complain of severe pain in the right leg. After three days the leg became cyanotic, moderately swollen and cold from the knee down. On December 6 the leg was black and cold; the toes were dry and there was complete loss of sensation downward from the lower portion of the upper third of the leg.

Hospitalization had been refused prior to December 7. On admission the temperature was 100° F. and the blood pressure 100/70. The abdomen was greatly distended but not tender. Fluids were given intravenously and subcutaneously, and amputation was done at the junction of the middle and lower thirds of the thigh several hours after admission. She recovered after a stormy convalescence, complicated by paralytic ileus.

CASE 2.—Mrs. A. S., aged 38, para ix; previous obstetric history not remarkable. She was delivered at full term on Oct. 25, 1932, by a midwife after being in labor for forty-eight hours. The membranes ruptured shortly after the onset of labor. She was first seen by a physician five days after delivery when she was having chills, sweats, fever up to 105° F., and foul lochia. On November 5 she began to complain of severe pain in the left leg and the extremity became tender and swollen. The temperature range continued high. On November 9 splotchy discoloration was noted over the foot and lower leg. Within forty-eight hours the foot and lower third of the leg were cold, of bluish black color and sensation was lost. A

REPORT OF CASE

CASE 1.—(No. 22193.) Mrs. E. H., housewife, aged 65 years, entered the hospital June 26, 1937, for the purpose of having a hysterectomy and vaginal repair for a third degree prolapse associated with a rectocele, cystocele, and enterocele. She had complained of pain and perineal irritation for years and had used a pessary for twenty, much of the irritation apparently had been due to the long continued use of the pessary. There has been some tendency to nocturia.

The family history is essentially negative and she has always made a good recovery from past illnesses. In March, 1922, she noted a lump in the right breast which started to increase in size in October of the same year and in two months it doubled in size. On Dec. 8, 1922, a radical mastectomy was performed by Dr. Deaver at the Women's Medical College Hospital in Philadelphia. Dr. Mollie A. Geiss reports that the tumor was diagnosed as a medullary carcinoma of the breast with mucoid degeneration and secondary involvement of the axillary nodes. Following this operation the patient remained in good health except that the right arm has maintained a size of some three times the normal, due to the circulatory and lymphatic block which followed the mastectomy. This finding on physical examination as well as the aforementioned profound prolapse constituted the only important physical findings, with the exception of a soft systolic murmur in the aortic area. The procidentia was so marked that on removing the pessary, and then having the patient cough, almost the entire uterus protruded from the introitus. The patient was somewhat obese, the pulse was 100 per minute and the temperature 98.6° F. Blood pressure was 195/105 mm.

The laboratory examinations showed a leucocyte count of 18,500, 4,230,000 erythrocytes and 84 per cent hemoglobin. The differential count on the blood smear showed polymorphonuclear leucocytes 70 per cent (of which 25 per cent were of the transitional type), 24 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophiles, and 2 per cent myelocytes. The Kahn test was negative. The urine contained a rare hyaline cast and 7 leucocytes and 2 erythrocytes per high power field; the specific gravity was 1.018, and there was a trace of albumin.

On June 28, 1937, under cyclopropane and avertin the enterocele was dissected out and repaired and a hysterectomy was done by one of us (R. L. M.). During the operation the uterus was found to contain pus, and a malignancy was suspected. The patient felt well following the surgery and steadily improved for ten days. At that time she began to have chills, a high fever (105° F.), and tenderness in the left lumbar region, the urine then became loaded with pus and urinary cultures showed both *Escherichia coli* and *Streptococci*; blood culture was negative. The patient again improved, but three weeks after the operation again began to lose ground and a nonprotein nitrogen determination on the blood on July 25 was 200 mg. On the next day the patient died.

Pathologic Report (A. A. H.).—The specimen consisted of a uterus which was enlarged three times its normal size and whose wall was soft and boggy. The cervix was attached and showed a transverse laceration. The cervix and the uterus were connected by a thin isthmus of tissue. There was an ulcerated patch near the internal os; part of the wall was soft but near the endometrial cavity it appeared very hard and firm with friable and feathery areas, from the gross appearance it could be seen that the indurated and ulcerative process had penetrated deeply into the wall. About 1 cm. above the internal os was an intramural yellow tumor which was the size and shape of a large cherry, it protruded or bulged above the surrounding myometrium which was only partially infiltrated with the indurated tumor in this area, and resembled both by touch and appearance ordinary adult fat. There were some small abscesses scattered in the invaded portions of the myometrium which measured a few millimeters in diameter. These were filled with white and gray pus.

Sections through the yellow tumor showed a typical adipose tissue structure which appeared quite sharply demarcated from the myometrium (see Fig. 1), some of the neighboring tissue showed small bits of the infiltrating tumor. This tumor in some areas showed a typical adenomatous structure and would be classified as an adenocarcinoma (Grade II), it possesses polypoid fronds as well which were sur-

LIPOMA OF THE UTERUS ASSOCIATED WITH CARCINOMA

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WHILE lipomas are common tumors and frequently met with in all portions of the body, even in such unusual sites as the kidney and central nervous system, they are exceedingly rare in the uterus. The rarity of this condition is emphasized by the paucity of reported cases and that with few exceptions,^{1, 2} these are on single cases. Moreover the only case in the Anglo-American literature seems to be that of Lund³ who mentions approximately 10 cases culled exclusively from the German literature. He notes that the first case reported was that of Bruning who described an intramural uterine lipoma in 1899, and in addition to his 10 cases we have found 7 others reported in the last two decades.^{2, 4-7} True lipomas have been reported also in the broad ligament,⁸ and Murray⁹ reports one weighing 17 ounces in the paravaginal region. In the uterus they may exist in almost any portion such as a leiomyoma might, and it is possible that they might extend into the ligaments or vaginal mucosa.

These lipomas resemble both histologically and grossly those in other regions and vary in size from a few millimeters in diameter to such a size that they suggest a pregnancy. This latter phase may be taken almost literally since the large tumors, being extremely soft, have been likened to the gravid uterus. Any symptoms arising from these tumors would merely simulate those caused by fibroids, that is, they depend very largely upon the size and location of the tumor mass, and as polypoid ones have been reported it can readily be seen that they might cause cramping pains and bleeding in much the same manner as a pedunculated sub-endometrial fibroid might. In two instances there has been a sarcomatous change^{3, 5} or more properly speaking, one of the lipomas was termed malignant, but to our knowledge the present case is the only one which has ever been reported in which the lipoma was associated intimately with an adenocarcinoma or other malignancy in the same site. Most of the writers agree that they are generally found in patients of advanced age, although this is somewhat shaken by Muschik's patient⁶ who was fifty-six years old.

Etiologically most writers agree that they are late developments of embryonic rests, but Gebhart³ described lipomatous areas in mixed tumors of the uterus, and Pollack³ thought that possibly some of the omental fat might have gained access to the uterine wall through some wound in its substance. There has also been some mention of a myxomatous degeneration in a leiomyoma producing a structure similar to a lipoma, a hypothesis that seems unsound and unaccepted.

Histologically, the tumors are usually sharply demarcated from the myometrium, although not definitely encapsulated. Merkel¹ noted in his case that unstriated muscle fibers extended directly from the wall into the central portion of the tumor, although this is unusual as most of the tumor sections can be described as merely typical lipomatous tissue. Grossly they appear as if they can be shelled out from the surrounding muscle and are yellow and greasy, resembling in every way the normal adult fat.

This case is also of interest because of the multiple tumors and what is obviously a fifteen-year cure of a carcinoma of the breast with involvement of the axillary nodes. Walkoff noted in his case of uterine lipoma that a lipoma of the left kidney also existed.³

Necropsy Report.—The heart was normal except for a very mild sclerosis of the coronaries and aorta. The lungs were adherent to the parietal pleura by firm adhesions throughout the upper lobes. The bases of both showed a decreased crepitus with increased consistency and on cross-section showed increased fluid and markedly decreased froth. The hilus nodes on both sides were calcified. The liver was yellowish brown in color and fat was detected in the scrapings. The spleen weighed 100 gm. and on cross-section showed an increase in connective tissue elements. The gastrointestinal tract appeared normal. The left kidney was enormously enlarged and occupied the greater part of the left side of the abdomen, and pus exuded through the fatty capsule, even before the kidney was removed. On cross-section it was made up of a number of large and small cysts which varied from pinpoint to walnut size; many of these were filled with pus and dirty fluid. The kidney measured 25 cm. in length and 15 cm. in diameter. The pelvis was filled with pus. The other kidney was somewhat smaller but the parenchyma had been replaced by cysts in the same manner, with the difference that these were filled with clear fluid, and there was no evidence of secondary infection. The bladder was somewhat injected and contained some purulent material. The old operative site showed a moderate injection and some minute abscesses. The left ureter traversed this area, but there was no apparent obstruction or lesion. There was no evidence of any metastases or metastatic glands, although some specimens were taken for sectional study. A very careful search was made in the right pectoral region and in the right axilla, but no evidence of recurrence of the old malignancy or enlarged or indurated axillary glands could be found.

Summary of Necropsy.—Bilateral polycystic kidney with a secondary inflammatory reaction in the left, resulting in a profound pyelonephritis. Terminal or hypostatic pneumonia of the lower lobes. Recent hysterectomy for proidentia and carcinoma of the uterus. There was no evidence of metastases in any area as a result of this malignancy or from the tumor of the breast which had been removed fifteen years previously.

DISCUSSION

This case is not only of interest because of the rarity of uterine lipomas, and because it is a proved case of a fifteen-year cure of carcinoma of the breast with axillary involvement, but also because it may, in a measure, explain the genesis of lipomas in this site as well as acanthoma. Ewing¹⁰ covers the controversy concerning the origin of this tumor excellently in his book citing both the exponents of the theory of multicentric origin and those of metaplasia. He states that a variable histogenesis may occur in adenoacanthomas of the cervix but that those in the uterus may be on the basis of metaplasia in almost all instances and do not require original heterotopia of squamous cells. We suggest, that in this case, the evidence pointing to the development of discrete but intermingled masses of adipose, squamous, epithelial, and adenomatous tissue, must rest largely in the favor of multiple heterotopia. For while the transition or metaplastic change from adenomatous tissue to squamous cell structures has been long recognized and is frequently seen in the cecum and elsewhere, the idea, that by similar metaplasia we may develop lipomatous tissue from these epithelial structures, is somewhat remote. It may be even possible that a single heterotopic focus might have harbored all of these various tissue structures, but as stated in the pathologic microscopic examination these tissues, while being in close apposition, did in no wise tend to merge into the other and were distinct and separate tissue entities. While not impossible, we cannot entertain the idea of the breast malignancy being the primary cause of the uterine malignancy. Such a site, without other evidence of visceral involvement, would be beyond the realm of reason and further, it is a well known fact that such lesions, if secondary, would never display such a completely different type of malignancy, for while we have not seen the sections of the original tumor, the description that was forwarded, places it in a vastly different category. This is merely one of the numerous cases of multiple primary malignancy.

faced by tall columnar cells. In other areas were masses and sheets of typical squamous epithelium with the irregular distribution through the muscle which characterized epithelial malignancies, many of these bits of acanthomatous tissue were in close apposition to the adenomatous portions of the malignancy, but there was a sharp division and no gradual gradation from one type of cell to another (see Fig. 3).

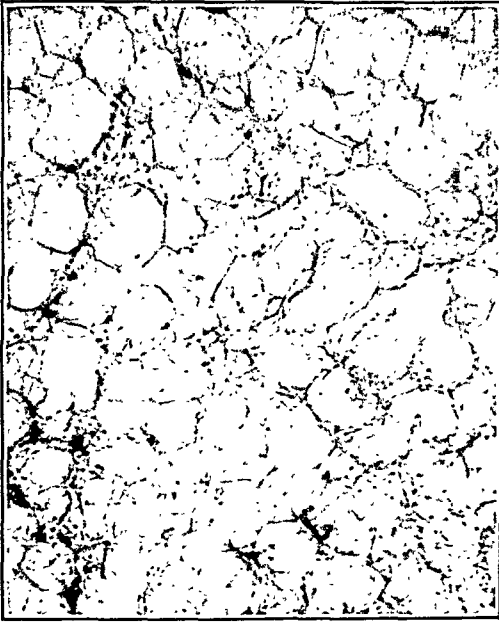


Fig. 1.



Fig. 2.

Fig. 1.—Section showing structure of the uterine lipoma. ($\times 125$.)

Fig. 2.—Cross-section of the uterus showing the lipoma. Note how it bulges above the surrounding myometrium. The cavity of the uterus is filled with the malignancy.



Fig. 3.



Fig. 4.

Fig. 3.—Section showing the adenoacanthoma, note the small islet of squamous cells near the center. ($\times 125$.)

Fig. 4.—Section of the myometrium showing a typical squamous cell area near the lipoma. ($\times 125$.)

Microscopic Diagnosis.—Adenocanthoma of the uterus associated with lipoma of the myometrium. Endometritis and abscess formation in the uterine wall secondary to the neoplasm.

ported on a base, in such a manner that the inlet makes an angle of 42 degrees with the horizon, which I have found from my studies² to be the average normal pelvic inclination in the recumbent posture.

Accessory parts which interfere with visibility, are eliminated from this type of manikin.

The skull, likewise, is a miniature of the theoretically perfect fetal skull originally designed by me. In it are incorporated such features as: (1) Normal relationship between the biparietal and bitemporal diameters. (2) Visible sutures and fontanels.

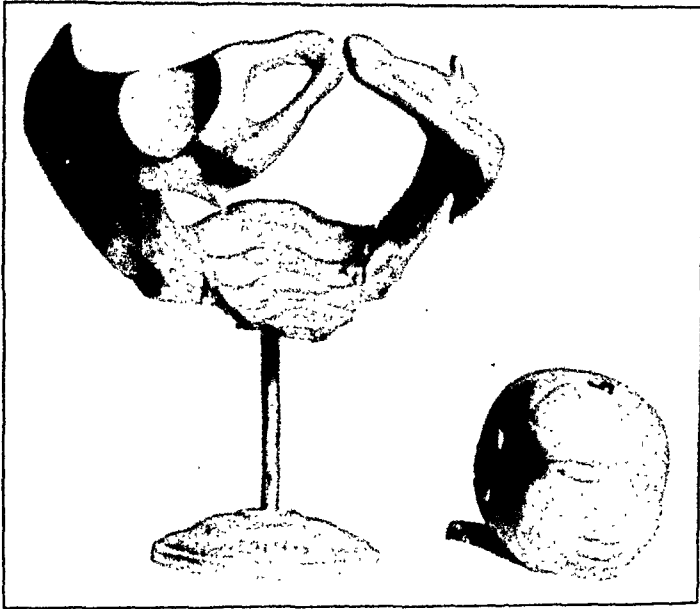


Fig. 1.

(3) Prominent malar bones, which play an important part in the mechanism of brow presentation. (4) The skull is so shaped, that slight deflection causes the sinciput to descend below the level of the occiput—a feature that is essential for demonstrating the cause of backward rotation of the occiput, in occipitoposterior presentations. (5) The neck, which serves as a handle, is so attached as to create a two-arm lever, the longer arm extending toward the chin.

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WASHINGTON MEDICAL BUILDING

Herold and Effkeman: The Significance of Hormonal Disturbances in the Origin of Cystic Mastopathies and in Epithelial Metaplasias of the Cervix, Zentralbl. f. Gynäk. 61: 1155, 1937.

Estrogenic hormones have a distinct influence on the development of tumors. This influence consists not of a disposition to stimulate tumors in general but only specific ones. However, such local growths arise only where there is a general tendency to tumor formation due either to hereditary factors, external factors or endocrine disturbances. The authors brought about changes in the cervix, uterus and breasts of animals by injections of estrogenic hormone. These changes resemble those seen clinically in human beings and considered to be precancerous.

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In passing, it is interesting to note that the hypertension is probably a result of the bilateral polycystic kidneys, an observation or finding which is not uncommon,¹¹ also that these cystic kidneys seem prone to be associated with various developmental errors in many cases and in this instance it is not unreasonable to regard the lipoma and even the two separate malignancies as developmental abnormalities.

SUMMARY

A case of lipoma of the uterus is presented which is associated with an adenocanthoma of that organ. It is felt that the three various types of tissue tumors in the one organ may lend some support to the theory of the multicentric origin from various heterotopia. Lipomas of the uterus are rare findings, this being the second report in the English language. Incidentally, the case is a proved fifteen-year cure of cancer of the breast with axillary involvement.

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A MANIKIN FOR INDIVIDUAL STUDENT USE

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THE idea of utilizing a metal manikin for teaching the mechanisms of labor in vertex, brow, and face presentations was advanced by me¹ some time ago. The model which was described in this JOURNAL has been sold at a price that made it possible for our school to install one in each of the six obstetric quiz rooms, the combined cost being no greater than the cost of one of the models that were formerly used. For use in my lectures to students and nurses, I have always carried one of these manikins in my car.

The efficiency of the device so impressed me that for many years I entertained the thought of producing a miniature that could be purchased for not more than the price of a textbook. This would enable the individual student to follow the mechanisms of labor in his own study.

Much disappointment was encountered, since I soon learned that pelvis removed from newborn babies were no larger than watch charms. Thus it was evident that such could not be used for modeling. After much difficulty I was able to procure pelvises from female children of various ages, only to meet with further disappointment. Pelvises of the size that I desired were not completely ossified and consisted of too many parts. Also, in contour, they could not be regarded as miniatures of the normal adult female pelvis, especially as regards the shape of the inlet, as well as all other characteristics.

The original model of the pelvis here presented (Fig. 1) was made by hand and is an exact miniature of the manikin that I had originally described and which is now in use in many of the medical schools. This manikin, made of aluminum, is sup-

Fetal Mortality.—Probably no complication of pregnancy is associated with a higher fetal mortality. In 1,012 cases the fetal death rate was 66.4 per cent. The lowest was 44.5 per cent. In a few small groups the fetal mortality reached 100 per cent.

TREATMENT

From a study of the various aspects of premature separation of the placenta, it becomes apparent that the therapeutic management of the condition must be almost equally as varied. No simple or specific therapeutic plan is applicable to all cases. Each case must be individualized and treated accordingly. Like gross obstetric hemorrhage in general, it is a major problem calling for mature judgment and wise guidance. Some one has poignantly stated that the fate of a patient suffering with grave obstetric bleeding is dependent largely on the first movement made by the attending physician.

Prevention.—In the practice of preventive medicine, no field is more fertile than obstetrics, and this is especially true with reference to the prevention of premature separation of the placenta.

Although the etiology of the complication is still somewhat obscure, the influence of toxemic disorders causatively, in a large percentage of cases, is almost universally accepted. It is, also, widely conceded that these conditions may largely be overcome by the assiduous practice of antenatal care. On this premise, it is reasonable to assume that measures directed antenatally toward the prevention of intoxication will diminish at the same time the incidence of placental separation.

Factors Influencing Treatment.—At the outset it must be borne in mind that the basic principles of management must be determined in each individual case. These are dependent on a large number of factors and may be considered under the following:

Condition of Patient.—In all instances it is incumbent, regardless of the type of treatment contemplated, either conservative or radical, that the age and parity of the patient, the presence or absence of toxemia, the condition of the cervix, the extent of bleeding with shock together with numerous other factors be seriously considered.

For example, in *elderly primigravidae*, especially in those cases associated with disproportion, it is clear that an expectant or conservative plan of therapy, delivery through the vaginal route, could by no means be considered favorably.

Parity must be considered equally, because it is well known that the death rate in multiparous is much greater than it is in primiparous patients, notwithstanding the observation that many more cases occur in multiparae than in primiparae. In Baird's series of 56 fatal cases, for instance, it was noted that 30 of the patients had 7 or more children, often in rapid succession.

The presence or absence of profound toxemia, particularly eclampsia, must always be seriously weighed before deciding on a definite plan of management. Patients with grave toxemia, notably the eclamptic patients, are poor subjects for major abdominal delivery, especially cesarean section.

Condition of Patient on Admission.—Because in many instances patients are admitted as emergencies, active treatment must be temporarily deferred and supportive measures instituted. Quiet and rest may be

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

TREATMENT OF PREMATURE SEPARATION OF THE PLACENTA

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PREMATURE separation of the normally implanted placenta is one of the most common as well as one of the most perilous complications of pregnancy. It occurs in about one-half to 1 per cent of all pregnancies and carries a maternal mortality of approximately 6 per cent and a fetal death rate of more than 60 per cent.

In this review of the available literature during the past five years, the period of gestation in the cases of premature separation reported was mentioned in 592 instances. The condition arose between the thirty-sixth week and full term in 334 or 56.4 per cent. In about 6 per cent complication developed just before the period of viability.

Reference was made to the etiology in 856 instances and pregnancy intoxication was accorded etiologically the predominant rôle in 611 or 71.9 per cent.

Maternal Mortality.—Premature separation of the placenta is not only responsible for a lamentably high maternal death rate, but for an especially high fetal death rate as well. In a study of 21 reports (Chart 1) comprising 2,319 cases, there were 145 maternal deaths, a mortality of 6.3 per cent.

In the collected case reports there is noted, however, a wide variation in the end-results, the maternal mortality ranging from nil in a series of 58 cases to 18.4 per cent in a group of 87 cases. These figures are not strictly comparable, because of the inclusion of varying periods of time. Obviously improved methods of diagnosis, as well as improved technical means of management, notably in recent years, have rendered a more favorable prognosis, especially for the mother.

The statistics of Baird as reported from the Glasgow Royal Maternity and Women's Hospital are especially impressive, because of the large number of cases cared for in a single institution. For the ten-year period 1925 to 1934 inclusive there were 1,160 cases, with a maternal mortality of 56 or 4.8 per cent. In this series of cases the results for the last five-year period did not show, however, improvement over the first five years, though it may be noted that the death rate for both was somewhat lower than the average.

Condition of Uterus.—The state of the uterine wall is still another fundamental factor to be included in the principles of management of premature separation. Bleeding, mild or extensive, into the myometrium commonly denominated uteroplacental apoplexy or the uterus "Couvelaire" (named for Alexandra Couvelaire who first described the lesion) is always an extremely grave complication. With extensive invasion of the musculature, uterine contraction with retraction may utterly fail and favor thereby continued bleeding following delivery. Since the more common practice of cesarean delivery, the uterus "Couvelaire" has been found not an infrequent accompaniment of the severe cases of accidental hemorrhage, notably those of the concealed type. Extensive hemorrhagic invasion of the uterine wall increases the gravity of the complication, the fetus is invariably destroyed and the maternal mortality is definitely elevated.

While there still exists some uncertainty as regards the disposition of the uterus in uteroplacental apoplexy, it is generally conceded that hysterectomy should follow section in cases associated with extensive involvement of the uterine wall and particularly if the uterus fails to contract promptly.

The Fetus in Uteroplacental Apoplexy.—Generally speaking, relatively little consideration can be given the fetus in the management of this complication, because, first, of the grave prognosis for the mother, and second, because of the enormously high mortality for the fetus, irrespective of the type of treatment instituted. The present survey has indicated that in about one-half of the cases the fetus is premature and frequently nonviable. Moreover, in a large percentage of instances the fetus is dead before the onset of labor, most commonly as a result of the associated toxemia. In the severe cases of separation, owing to acute placental insufficiency, fetal death occurs before or shortly after the onset of labor. Unfortunately, the type of delivery most favorable for the fetus prognostically, namely, cesarean section, is undertaken generally in the severe cases in which the baby is already dead or the outlook for its survival extremely discouraging.

Active Treatment.—From what has been said thus far regarding therapy, it becomes at once apparent that no specific mode of management is applicable to all cases. Every case of premature separation, as a matter of emphasis, is an individual problem, calling for the most discriminating judgment in deciding on a therapeutic plan.

The complication should by no means ever be regarded as a *simple or ordinary problem and, hence, its solution does not come within the province of the ordinary man.* Immediate hospital care should be provided for all patients and all should receive the wise guidance and superior technical training of a skilled accoucheur.

The chief objectives in active treatment are two: first, the prompt delivery of the child with the detached placenta and, second, control of the bleeding. As a rule, with the extraction of the products of conception, further bleeding, of course, is effectively taken care of at the same time.

Combined with the foregoing, it is imperative in all cases that continued loss of blood be prevented by uterine tamponade following delivery from below and by hysterectomy following delivery from above, particularly in those cases associated with a hemorrhagic musculature and lack of uterine contractility.

afforded by the administration of morphine and blood loss restored by immediate blood transfusion. *In every case* this recourse should be adopted before, during, or immediately after delivery. As a temporary expedient, saline or glucose solution may be administered by hypodermoclysis or venoclysis. In numerous instances it has been definitely determined that the omission of blood transfusion in the management of late antenatal hemorrhage, arising especially from placenta previa and premature separation, was responsible for an increase in the death rate of almost 50 per cent. The transcendent value of blood transfusion may be appreciated when it is recalled that hemorrhage with shock is the chief cause of death in the great majority of cases.

Besides the foregoing, every means should be adopted to prevent further blood loss before, during, and after delivery, by either vaginal or uterine tamponade, observing every precaution, of course, to avoid contamination.

Next to hemorrhage with shock, septic infection ranks as the most common factor in mortality. Therefore every effort should be observed to avoid vaginal manipulation, except under the guidance of every possible aseptic safeguard. *It is a growing conviction that in all pregnant women after the thirty-sixth week of gestation the vaginal canal should, metaphorically speaking, be regarded as a hermetically sealed tube.*

Progress of Labor and Condition of Cervix.—The progress of labor, particularly with regard to the degree of cervical dilatation, is of fundamental importance in determining whether delivery should be accomplished by the vaginal or abdominal route.

With the cervix completely dilated and with the presenting part, vertex or breech, in the lower reaches of the vaginal canal, conservative forceps delivery or extraction may be practiced. With the cervical canal, on the other hand, uneffaced and only partially dilated or scarcely dilated at all, the far more preferable plan is delivery by low cesarean section. This in brief is the attitude most widely advocated and practiced in the treatment of premature separation, especially with relation to the cervix, today.

Type of Hemorrhage.—Another determining factor in the plan of management is the type of hemorrhage encountered.

In mild cases of "revealed" bleeding, provided local or cervical conditions are favorable, conservative measures may occasionally be instituted. Temporary control in cases falling in this category may be afforded by *aseptic* cervicovaginal tamponade combined with the application of a firmly fitting abdominal binder (Spanish windlass).

In "concealed" hemorrhage a more radical plan is imperatively indicated. In cases of this type abdominal delivery with generous blood transfusion should be adopted forthwith. Because it may progress with exceeding rapidity and without being readily recognized, concealed hemorrhage is most grave.

Condition of Placenta.—Obviously it would be of great advantage in deciding on a plan of treatment if one could determine the exact state of the placenta, or, in other words, the extent of its separation. This, naturally, is well nigh impossible.

If complete separation is suspected or recognized, immediate delivery, preferably by the abdominal route, is called for. The unfavorable condition, however, of the patient, often a complicating feature of the grave types of separation, may render prompt radical measures unpropitious or even impossible.

Radical treatment has been variously defined. It was observed in many of the reports studied that numerous measures were described including some of the simple obstetric maneuvers, as well as those of a more formidable character. For the sake of uniformity, we have incorporated in this division all manipulative procedures practiced vaginally.

The high mortality associated with the radical plan of therapy was due in great measure to the various types of vaginal manipulation and instrumentation including chiefly: a. Forceful dilatation of the cervix, b. Braxton-Hicks version, c. podalic version, d. extraction, e. embryotomy, f. the high application of forceps, and g. bagging.

To emphasize the part played in the mortality by methods of this nature, mention may be made of 6 deaths following 11 attempts at manual or instrumental cervical dilatation.

This method when contrasted with the simple expedient of puncturing the membranes indicates that it rarely should be considered in the management of premature separation. For example, in 35 cases of placental separation with only two deaths, simple rupture of the bag of waters was the only means employed.

In the reports emanating from the Irish Clinics, puncture of the membranes was noted as the most frequent form of obstetric intervention employed, with favorable results. Thus among 134 patients treated by conservative methods, the maternal mortality was only 8.4 per cent in contrast with an average mortality of 17.6 per cent in 153 patients treated conservatively in various other institutions.

Braxton-Hicks version and internal podalic version, with or without extraction, were employed in a small number of cases. Objection to these measures is based on the observation that not infrequently they add to the shock and favor infection.

Cervicovaginal tamponade is still recommended, but the use of the bag is gradually being abandoned, because in so many instances it proved ineffective and because of the risks of sepsis.

Of more than passing interest is the policy pursued in the large Irish maternities mentioned. In these institutions every effort is made to allow labor to progress along normal lines. Treatment is generally limited to the employment of routine supportive measures, especially the use of elysis, transfusions, morphia, and binders. Where intervention is practiced, it is along the simplest lines, using measures associated with the least amount of trauma and shock, as puncture of the membranes, cervicovaginal tamponade and, in severe cases, the delivery of a leg. It is notable that in the 278 cases reviewed from these institutions not a single abdominal delivery is recorded. The maternal mortality rates were well within the average combined percentage. However, it may be questioned whether the mortality may be further lowered without the use of radical procedures in the frankly severe cases.

The increasing employment of abdominal delivery in the treatment of premature separation was quite apparent in most of the articles studied. Most authors seem to agree that it is the method of choice in the following circumstances:

1. In cases associated with acute or violent bleeding.
2. In cases associated with extensive concealed hemorrhage.
3. In cases of complete separation.
4. In cases with the cervix long, uneffaced and undilated.

In the mild case, very little or no interference at all is practiced locally, delivery being allowed to take place spontaneously or promptly brought to conclusion by forceps in vertex and extraction in breech presentations, provided, of course, the local or cervical condition is conducive to measures of this character.

In most of the papers studied in the present survey, the methods of delivery were classified as follows: Expectant, radical, surgical (cesarean section).

A comparison of the ultimate results following the adoption and practice of the foregoing methods disclosed that in most instances the mild cases were treated expectantly and more severe cases by some form of interference.




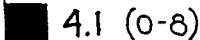

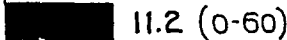



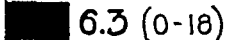
 Fetal mortality %	() Mortality range %	No. of patients
 Maternal mortality %		
EXPECTANT TREATMENT		
 60.7	(0-83)	414
 4.1	(0-8)	
CESAREAN SECTION		
 74.4	(56-100)	107
 11.2	(0-60)	
RADICAL TREATMENT		
 73	(0-100)	284
 13.4	(0-31)	
ALL TYPES OF TREATMENT		
 66.4	(55-100)	2319
 6.3	(0-18)	

Chart 1.—Analysis of 2,319 cases of premature separation of the placenta, from representative clinics.

In many clinics, our study revealed that attempts were made to deliver almost all patients by a uniform or standard method of procedure.

The final results in the 805 patients studied in the present survey with regard to the type of treatment showed a maternal mortality of 8.4 per cent. These figures disclosed further facts of special interest: The mortality was lowest among those patients who were treated expectantly. In this group there were 414 cases with 16 deaths, a mortality of 4.1 per cent. The highest maternal death rate occurred in the radical group. Here there were recorded 284 patients with 38 deaths, a mortality of 13.4 per cent. Surgical methods yielded an intermediate mortality of 12 or a percentage of 11.2 in 107 patients.

A difference in the final outcome in the three different forms of management is quite impressive, but the comparison between the radical and surgical methods instituted is especially significant.

The patients treated by these two methods, radical and surgical, were those in whom the bleeding was of an acute type and in whom active interference was deemed imperative.

other means, is not ardently advocated nor practiced; first, because of the attendant dangers and, second, because of its far greater mortality.

6. In cases of premature separation arising in elderly primigravidae, especially if associated with cephalopelvic disproportion, the low cesarean section is accorded the treatment of choice.

7. The same recourse is regarded as the preferential plan in cases associated with an uneffaced and undilated cervical canal.

8. With the cervix completely effaced and dilated, combined with bleeding of a mild or moderate character, expectant measures, including puncture of the membranes, the application of a cervicovaginal tamponade together with a tight abdominal binder may be used.

9. In cases of an acute or violent character, accompanied by widespread hemorrhagic changes in the uterine wall and a lack of contractility, hysterectomy following delivery is favorably commended and practiced. On the other hand, the uterine body, provided the hemorrhagic infiltration is slight and with contractility present, may be retained.

10. It has been demonstrated most impressively that blood transfusion with hypodermoclysis or venoclysis before, during, and after delivery, in addition to other restorative measures, must be regarded as indispensable agencies in the therapeutic regime of all cases of premature placental separation.

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Winterton, W. R.: Continuous Drip Transfusion in Gynecology and Obstetrics, *J. Obst. & Gynaec. Brit. Emp.* 44: 510, 1937.

The total quantity of blood in the average adult is approximately 10 pints. The customary transfusion of a pint of blood can do no more than raise the hemoglobin of the recipient by 10 per cent. In a severe case of anemia, such as an exsanguinated case of fibroids, the total hemoglobin after transfusion may still be less than 30 per cent. Recognition of this fact is the basis of drip blood transfusion. The amount of blood to be given in drip blood transfusion should be sufficient to restore the hemoglobin to the neighborhood of 80 per cent. This idea, however, may necessitate in grave anemia transfusions not far short of a gallon.

The introduction of such amounts by ordinary methods would result in gross increase of the blood-volume causing cardiac failure consequent upon overloading of the circulation. To overcome this difficulty the slow drip method was evolved.

A rate of 40 drops per minute is equivalent to a pint in four hours, i.e. a rise of 10 per cent of hemoglobin in an adult. This rate should be regarded as the maximal permissible rate of administration to a nonbleeding patient who is to receive several pints. In a patient who is bleeding the hemoglobin should still be increased by 10 per cent over four hours.

These large transfusions obviously necessitate a number of donors for each case. Little difficulty in obtaining donors has been experienced since the adoption of the practice of putting the onus of responsibility firmly upon the relatives. All donors must be of the same group as the patient and as each other.

J. P. GREENHILL.

5. In cases arising in elderly primigravidae, especially in those with disproportion.
6. In cases displaying symptoms and signs of hemorrhagic infiltration of the myometrium.
7. In cases associated with tardy labor.

The end-results following routine cesarean delivery in the type of cases herewith enumerated were considerably more encouraging than the results following other methods of treatment in cases of a similar type. Nevertheless, it must be emphasized that the mortality rate following cesarean delivery in premature separation of the placenta (11.2 per cent) is more than twice as high as the accepted mortality of cesarean section in general.

The classical section was the most common type of operation performed. Low cesarean section figured prominently in the reports of many writers who are deeply convinced it should be used far more frequently in the treatment of this grave complication of pregnancy. This conviction is based on the observation that the maternal mortality is much lower following the cervical than the classical procedure.

Reference has been made previously to the disposition of the uterus in violent cases of premature separation. It is quite generally acknowledged that hysterectomy always should be performed, first, if the organ fails promptly to contract and, second, if the myometrium is infiltrated extensively with blood.

SUMMARIZATION

From the foregoing extensive survey of the available literature dealing with premature separation of the placenta for the five-year period, 1932 to 1936 inclusive, the following summarization may be made:

1. In a series of 249,331 deliveries, there were 2,319 cases of premature placental separation, an incidence of 0.93 per cent. It will be observed that the incidence is approximately 1 in 100 deliveries. In private practice it may be somewhat less and in hospital practice somewhat more than 1 per cent.

2. Premature separation of the placenta prognostically is one of the most perilous complications of pregnancy. It is associated with a maternal death rate of more than 6 per cent and a fetal mortality ranging from 45 to 100 per cent, and averaging about 70 per cent.

3. Since the cause of the condition is not definitely known together with the presence concomitantly of grave complicating conditions in many instances, pregnancy toxemia especially, it is obvious that no specific type of treatment is applicable to all cases.

4. The active treatment of premature separation is customarily classified into: Expectant, radical, surgical (cesarean section).

The expectant form of treatment employed in conjunction with supportive measures has proved most satisfactory in the management of the milder cases and is associated with the lowest maternal mortality rate. In the treatment of the severe cases, radical surgical treatment was very definitely superior.

5. The second, the radical plan, embracing various forms of obstetric maneuvers, as dilatation of the cervix, manual or instrumental, bagging, the high application of forceps, combined and podalic version, as well as

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Sterility

Caslier, P.: Studies on the Mode of Transportation of the Human Ovum, Zentralbl. f. Gynäk. 60: 1873, 1936.

The author presents clinical and experimental evidence that following the injection of prolan given in a dose of 3,400 rat units there will be found at the tenth and eleventh days of the cycle, an immediate apposition of the fimbriated end of the Fallopian tube on the rupturing or ruptured Graafian follicle. He believes that by means of this injection a situation is created which closely corresponds to the physiological process.

On the basis of his observations the author concludes that when the follicle ruptures, or immediately before, the fimbriated end of the Fallopian tube covers the rupturing follicle so that at the instant of rupture the ovum and the follicular fluid are injected directly into the ostium abdominale of the tube.

The ovum is conveyed into the desired direction mainly by the muscular action of the pars isthmica of the tube and in this mechanism the fimbria ovarica plays probably the important role. It is readily seen that for proper functioning of this mechanism, free mobility of the Fallopian tube is essential and it is therefore important, in certain cases of sterility, not only to ascertain the patency of the tube but also to restore its free mobility.

RICHARD E. SOMMA.

Daniel, Nitescu, Solmaru, and Georgescu: Study of the Physiology of the Fallopian Tubes in Women, Rev. franç. de gynéc. et d'obst. 32: 421, 1937.

For pregnancy to occur, it is necessary not only that the Fallopian tubes be permeable but also that they possess the power to contract in order to direct the ovum toward the uterine cavity.

They experimented with 25 human tubes removed at operation and found: that tubal contractions began at the ampulla and were directed toward the uterine end; that nicotine in small doses increased the tonicity of the tubes but in large doses suppressed the contractions and paralyzed the tubes. In the presence of nicotine, adrenalin no longer was able to excite transitory tubal activity. Small doses of pituitary had no effect but large doses diminish the tonicity and frequency of tubal contractions. Prolan sensitizes the tubes to the effect produced by estrin. Corpus luteum also reduces tubal tonicity.

J. P. GREENHILL.

Te Groen, L. J.: Some Aspects of Sterility, South African M. J. 11: 725, 1937.

A detailed history of the marital relationship is essential. Dyspareunia, whether primary or secondary, requires attention. Treatment must be directed at the cause of the lesion. The general investigation of a sterility case is followed by examination of the semen shortly after coitus. The frequency of sterility due to the husband varies between 20 and 60 per cent.

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF OCTOBER 7, 1937

The following papers and discussions were presented:

Uterine Bleeding With Virilism. Dr. Virginia G. Rheuby (by invitation). (For original article, see page 119.)

The Potential Bisexual Character of the Ovary. Drs. A. J. Ramsey and J. F. McCahey (by invitation). (For original article, see page 111.)

Virilism and Female Pseudohermaphroditism With Relation to the Bisexual Nature of the Ovary. Drs. J. F. McCahey and A. J. Ramsey (by invitation). (For original article, see page 104.)

NEW YORK OBSTETRICAL SOCIETY

MEETING OF OCTOBER 12, 1937

The following papers were presented:

The Female Pelvis as a Focus of Infection in Arthritis. Dr. David N. Barrows.

The Effect of Estrogenic Hormone Upon the Contractility of the Fallopian Tubes. Drs. Samuel H. Geist, U. J. Solomon, and M. E. Mintz. (For original article, see page 67.)

Thiele, George: Coccygodynia, J. A. M. A. 109: 1271, 1937.

Coccygodynia was found to be accompanied by spasm of the levator ani and/or coccygeus muscles in 64 of 69 patients seen by 9 different observers.

Spasm of the piriformis muscle was found in 31 of 33 patients with pain in the suprapluteal region or down the back of the thigh.

In a series of 80 patients treated by massage by 8 different proctologists 60 per cent were cured, 33.7 per cent were definitely improved and 6.3 per cent were unimproved.

On digital rectal examination, with the patient in the Sims position, spasm of the levator is easily detected by lateroposterior pressure. The piriformis muscle is felt with the tip of the finger just distal to the sacrospinous ligament. It is most easily felt on the right side when the patient is lying on the left side and vice versa.

In all cases a uniform technic of massage has been used. With full length insertion of the finger in the rectum, lateroposterior pressure will place its flexor surface horizontally across the surfaces of the levator ani and coccygeus muscles almost at a right angle to their fibers. These muscles are massaged in the long direction. Massage is begun lightly. If definite improvement does not result after the first four to six massages over a period of a week or ten days, orthopedic or other indicated consultation should be sought.

GROVIE LIESE.

maximal point of fertility. We may presume that like in animals also in the human female some variability occurs in this position. As far as we know, gametes of the human species retain the factor of fertility only for a short period. Therefore, fertilization must follow in close sequence to cohabitation, assuming that only one ovum is produced in each cycle. Absolutely regular cycles are uncommon. Unexpected irregularities in menstruation can occur at any time. Hence, one must doubt the infallibility of the Ogino-Knaus theory of a "safe period," even if applied only in the strictest sense of limiting it to known cycles of minor variabilities.

Popularization of the thought of a safe period is prone to bring much unhappiness. The problem still is subject to debate and the laity should be informed that the matter is not settled.

HUGO EHRENFEST.

Béclère, C., and Francois, E.: Chronic Genital Infection in the Etiology of Persistent Sterility in the Female, Bull. Soc. d'obst. et de gynéc. 26: 709, 1937.

Of 110 cases of sterility of the female studied by the authors, only 11 of the patients became pregnant. In almost half of the remaining 99 women, both tubes were completely closed. In more than three-fourths of them the tubal obstruction was due to chronic genital infections and in nearly two-thirds of these cases the causative organism was the gonococcus.

In one-fourth of all the sterile women the tubes were patent but the lumen was markedly constricted. In over three-fourths of these cases, the cause of this was a chronic pelvic infection but the gonococcus was responsible for only one-third of these infections.

In the remaining one-fourth of the authors' sterile women, the tubes were normally patent. However, frequently the permeability could not be determined at the time of examination or only after using very high pressures. Likewise in these cases chronic pelvic infection was found in three-fourths of them. A positive gonococcus reaction was obtained in one-half of these cases.

J. P. GREENHILL.

Graf, A.: The Fertility of Women After Amputation and Paquelin Treatment of the Cervix Performed for Erosions and Elongation of the Cervix, Monatschr. f. Geburtsh. u. Gynäk. 105: 272, 1937.

Many authors have reported that miscarriages and sterility follow amputation of the cervix. Therefore Graf undertook to follow up all the patients who had cervical amputations at the Düsseldorf Woman's Clinic since 1928. He found 21 such cases. Only 4 of these women subsequently became pregnant while the other seventeen remained sterile in spite of good cosmetic results. In the same period of time 25 women were treated with the Paquelin cautery and none of these subsequently became pregnant.

The author explains the sterility which follows amputation of the cervix as follows: Normally the cervical secretion, which is alkaline, bathes the upper part of the vagina. This produces a favorable medium for spermatozoa. When the cervix is removed, this alkaline secretion is missing and the sperm cells come to rest in an unfavorable acid medium. Furthermore, the spermatozoa have difficulty getting into the uterine cavity because there is no cervix dipping down into the posterior vaginal fornix.

J. P. GREENHILL.

Weiser, Frances J.: The Relationship of Contraception to Sterility, J. Contraception, 2: 78, 1937.

Medical writers occasionally have stated that the prolonged use of any preventive measure may produce relative sterility, i.e., may delay conception. Weiser investigated this problem from clinical records and now presents the following findings: The contraceptive prescribed at the clinic had been employed by these women for from three to forty-two months before pregnancy was decided upon.

The conditions of hypermenorrhea and polymenorrhea play a part in sterility, as well as vitamin deficiency. Diagnostic curettage is a valuable therapy for sterility. Ovarian dysfunction and uterine displacement require treatment. Insufflation and lipiodol injection of the tubes are becoming routine procedures to determine patency of the tubes. Injection of hormones, x-ray irradiation of the hypophysis and ovaries have their indications, as well as artificial insemination with husband's or donor's semen.

F. L. ADAIR AND S. A. PEARL.

Gierhacke, E.: The Fertility Vitamin E, *Klin. Wehnsehr.* 15: 221, 1936.

Vitamin E which controls fertility has heretofore been neglected clinically. Its use therapeutically in England, Switzerland, and Denmark in both human and veterinarian medicine has led the author to conduct a series of experiments which he describes in detail. This experimental work convinces him that vitamin E is most essential for the completely efficient reproductive life of both humans and animals. He is convinced that the administration of vitamin E is essential in the treatment of habitual abortion, primary sterility in the female and also in sterility of the male when this latter is not neuropathic in origin. The future, therefore, holds a rational form of therapy that should prove highly successful in these types of reproductive disorders.

RALPH A. REIS.

Albrecht, B.: Periodic Fertility and Sterility, *Arch. f. Gynäk.* 161: 23, 1936.

There is an orderly and regular cycle of fertility and sterility in woman which is controlled by the biologic processes. This results in definite "fertile" and "sterile" days. The fertile days are linked with ovulation and are therefore the twelfth to the sixteenth days preceding the next menstruation. Two to three days preceding the above-mentioned days must be included since this represents the duration of fertilibility of the sperms.

It is absolutely impossible to determine the relatively sterile days with mathematical accuracy because of the well-known irregularities and variations of the normal menstrual cycle. Ovulation frequently is early and just as frequently is delayed.

However, the author believes that many of the sterile couples under treatment can be helped by an accurate determination of the fertile period and by careful instruction as to the optimum time for fruitful coitus.

RALPH A. REIS.

Guthmann, H., and Vetter, H.: The Question of Temporary, Physiologic Sterility Among Women, *Monatschr. f. Geburtsh. u. Gynäk.* 104: 129, 1937.

The authors investigated the relationship of the time of conception to the menstrual period in 146 carefully controlled cases. They found a definite accumulation of pregnancies at a particular time in the cycle but nevertheless there was a wide spacing of conception in the menstrual cycle. Pregnancy was possible not only in the midinterval period but also just before and shortly after the bleedings. The authors insist that the use of the so-called safe period is not a substitute for operative or radiologic sterilization in cases where sterilization is indicated for medical or eugenic reasons.

J. P. GREENHILL.

Emge, Ludwig A.: Is the So-Called "Safe Period" Trustworthy? *Western J. Surg.* 44: 28, 1936.

A careful analytical study of all available data leads the writer to various conclusions, among them the following: There no longer can be any doubt that the period of conception includes minimal and maximal possibilities in each menstrual cycle, regardless of the divergence of opinions regarding the exact position of the

a slide. After drying, the film is fixed with heat, and stained with a modified Wollschwartz solution, washed with water and counterstained with Loeffler's methylene blue. This stain imparts a dull grayish color to every thing except the heads of the spermatozoa; the latter stand out as bright golden or yellowish spots in this gray background. The stain is exceptionally selective for spermatozoa; the spermatozoon heads maintain their morphologic characteristics indefinitely. The stain further serves to identify spermatozoa of different species as well as of different individuals of the same species.

W. B. SERBIN.

Donay: Hysterosalpingography and Its Dangers, *Bull. Soc. d'obst. et de gynéc.* 25: 514, 1936.

Since 1927 Donay and his associates have made 1,409 hysterosalpingograms. The fact cannot be denied that the procedure is dangerous. Furthermore, in his opinion, the interpretation of the films is more difficult than the operation itself. Even after years of experience, mistakes can be made in interpreting the x-ray plates. By means of a special apparatus the author has obtained good results. He mentions a number of abnormal occurrences especially injection of lipiodol into the peritubal tissue and into the veins of the uterus, and from these into the large veins. Serious complications may arise when lipiodol is employed in the presence of an open hydrosalpinx because occasionally the retained substance transforms the hydrosalpinx into a pyosalpinx. In four of the author's cases infection resulted in such cases. In one patient, an abscess was opened by colpotomy and in two other patients hysterectomies had to be performed.

Because of the risks of lipiodol the author first employs the Rubin test in cases of sterility.

J. P. GREENHILL.

Mocquot, Palmer, Lejeune, and Razi: Hystero-graphs With Lipiodol Controlled Manometrically With Low Pressures, *Bull. Soc. d'obst. et de gynéc.* 25: 519, 1936.

The authors found that after injection of lipiodol into the uterus, contractions of the latter were useful but not indispensable for the propulsion of lipiodol into the tubes. If a pressure of 5 to 7 cm. Hg was used, lipiodol entered the tubes but if only 4 cm. of pressure was used, the oil remained in the uterine cavity. This is very important to know because when lipiodol is injected into the uterus in cases of carcinoma it is most important to avoid getting lipiodol into the tubes.

J. P. GREENHILL.

Margraf, B.: Tubal Insufflation and Salpingography, *Arch. f. Gynäk.* 161: 135, 1936.

The author reports a series of 160 women in whom tubal insufflation, salpingography or both were done for sterility. In 122, the tubes were patent but only 22 became pregnant subsequently. One of these and four of those with tubes closed developed tubal pregnancies and 17 carried the pregnancy to term. Tubal insufflation with or without hysterosalpingography probably has definite therapeutic as well as diagnostic value in the treatment of sterility. The author calls attention to the high incidence of tubal pregnancy following these procedures.

RALPH A. REIS.

Brault, P., and Tizon, A.: Hysterosalpingography and Sterility, *Bull. Soc. d'obst. et de gynéc.* 26: 262, 1937.

The authors report their results in 50 cases of hysterosalpingography performed in sterile women. Sixteen of these women (32 per cent) became pregnant. Of these 16 women, 13 had living babies, 2 had abortions and 2 had ectopic pregnancies. In the patients who had the ectopic pregnancies, the tubes appeared abnormal on the x-ray

More than 50 per cent had used the method for one year or longer. After discontinuation of contraception impregnation occurred in 50 per cent within the first month, and in a total of 65 per cent within three months. Of the women using protection for a year or more better than 55 per cent conceived within three months after planning a pregnancy.

Contraceptive measures as prescribed by this clinic apparently do not play any role in the causation of sterility or in the time required for conception.

HUGO EHRENFEST.

Huhner, M.: *The Huhner Test in the Diagnosis of Sterility Due to Necrostermia*, Japanese J. Obst. & Gynec. 19: 508, 1936.

The up-to-date gynecologist very wisely refuses to treat a woman for sterility until satisfied that the husband is not at fault. He therefore first examines several condom specimens (one is not enough) and if he persistently finds only dead spermatozoa, he instructs the patient to have her husband examined by a urologist and treated for this condition.

Many years ago Huhner made a series of experiments which showed that virulent gonococci do not interfere with the vitality of spermatozoa and are not therefore a cause of necrostermia. Whenever gonorrhea causes sterility, it is due to the pathologic changes brought about in either sex by the gonorrheal inflammation (occlusion of the vas in the male or closure of the Fallopian tubes in the female).

Huhner for many years called attention to an artificial necrostermia which is not uncommon. He refers to those cases in which the patient, fearing that the condom specimen would become cold before it reaches the doctor, either puts the condom in a jar of supposedly warm water or else places the condom wrapped in a towel underneath a hot water bag or on a hot radiator. In these cases the heat is too great and all the spermatozoa are killed at once. For this reason Huhner for years advised his patients not to use any heat at all in connection with the condom specimen. At times also the powder, which manufacturers place into condoms to help their easy application, has a detrimental effect on the vitality of the spermatozoa.

Huhner has seen quite a few cases in which he has examined many condom specimens with all the precautions previously mentioned, and in some cases as early as twenty minutes after coitus, and always found only dead spermatozoa in the condom and yet a post-coital examination (Huhner Test) revealed very many, very lively normal spermatozoa in the wife's vagina. In some of these cases the spermatozoa removed from the female genitals after coitus remained alive for several hours under the microscope while in the condom specimen they were found dead within twenty minutes.

J. P. GREENHILL.

Ranson, R. M.: *Rubber and Sperm-Survival*, Lancet 1: 1400, 1937.

A study was undertaken to determine the spermicidal potency of rubber sheaths. The specimens were collected in sheaths, immediately transferred to glass tubes and transported to the laboratory. There 0.5 cm. of semen was transferred to the sheaths of the tests and kept at 37° C. In control tubes the sperm remained at full activity for five hours. In highly spermicidal sheaths all sperms were dead in three-quarters of an hour. The most spermicidal sheaths appear to be latex rubber and the least those made of molded rubber.

H. CLOSE HESSELTINE.

Williams, W. W.: *Examination of Suspected Semen Stains for Spermatozoa*, J. Lab. & Clin. Med. 22: 1173, 1937.

Spermatozoa, when dried on clothing or elsewhere, maintain their morphologic characteristics and staining properties over long periods of time. This fact is of medicolegal importance. The following technique has been found useful in demonstrating spermatozoa: A small piece of the soiled cloth is treated with two drops of saline solution and with a blunt edge of a scalpel the surface is scraped upon

Kuestner, H.: Results of Salpingostomy, *Arch. f. Gynäk.* 161: 135, 1936.

The author reports the collected statistics from 37 clinics. This group includes 93 operations of reimplantation of the tube into the uterus. In the majority of cases, this was carried out on both tubes. There was one death from embolism. Ten patients complained of severe dysmenorrhea following the operation. Postoperative tubal patency tests on 50 of these patients showed at least one patent tube in twenty. While in the remaining 30 patients both tubes were found closed. Ten patients had subsequent pregnancies; of these 2 miscarried and 8 were delivered of full-term babies. A patient has, therefore, only a 10 per cent chance of achieving a pregnancy as a result of this type of operation.

RALPH A. REIS.

Green-Armytage, V. B.: Tubo-Uterine Implantation for Sterility Followed by Full-Term Pregnancy, *Brit. M.* 2: 6, 1937.

A successful case is reported of the use of tubal implantation in the treatment of sterility in a patient who had previously been sterilized by tubal resection. A modified Bonney technique for tubal implantation is described. The author encourages the adoption of this procedure rather than salpingostomy. The technique is simple, and complete hemostasis is obtained by clamping the cervix and using a ring forceps on the infundibulo-pelvic ligaments.

This operation is useful whether the occlusion of the tube is at the fimbriated or at the cornual portion.

F. L. ADAIR AND S. A. PEARL.

Hartmann, K.: Tubal Changes Following Madlener Sterilization, *Arch. f. Gynäk.* 162: 407, 1936.

Careful serial sections were carried out by the author on four sets of uterine tubes which were removed at varying intervals following sterilization by the Madlener method. Findings are described in detail, the most characteristic change being a complete hyalinization of the loop. In none of the tubes studied was the lumen patent nor could any fistulas be demonstrated. The author therefore believes that failure following the Madlener type of sterilization is not due to the method but rather to the faulty carrying out of the exact technique. Such failure is caused by insufficient crushing of the loop.

RALPH A. REIS.

Gerloff, Klaus: Advances in the Treatment of Sterility, *Zentralbl. f. Gynäk.* 60: 2365, 1936.

Gerloff reports the results obtained in 102 women treated for sterility. No cases were included in which sterility was due to severe hormonal disturbances. In 16 cases, treatment resulted in pregnancy which corresponds to 15 per cent of the total cases.

The author believes that better results would be obtained if the true cause of sterility could be determined in every case. In the majority of cases, however, sterility probably is due to multiple factors.

RICHARD E. SOMMA.

Van Tongeren, F. C.: Uterine Probing as a Simple Means of Treatment of Sterility in the Female, *Arch. f. Gynäk.* 161: 143, 1936.

The author has been carrying out probing of the uterine cavity as a simple means of treating sterility in women for many years. He states that it is a harmless procedure when done under strict asepsis. The optimum time for using it is the tenth day of the menstrual cycle—which is just before ovulation.

plates and the authors had given these patients an unfavorable prognosis. The authors did not observe any bad effects from the hysterosalpingography.

J. P. GREENHILL.

Bonnet, L.: Kymographic Tubal Insufflation, Bull. Soc. d'obst. et de gynéc. 25: 666, 1936.

The author has employed tubal insufflation since 1922. A few months ago he reported his results with this procedure and reported an 18.4 per cent incidence of pregnancy following its use. He has given up the ordinary method of carrying out a tubal patency test and now employs the kymographic method recommended by Rubin.

By means of a kymographic record one can differentiate between a tube which is normally permeable, which is impermeable, which is undergoing spasm or actually stenosed, that is a tube whose lumen is more or less constricted due either to external or internal causes.

During the last few years Rubin has demonstrated that there exists a relationship of cause and effect between the hormonal function of the ovary and the peristaltic movements of the Fallopian tubes. Hence analysis of the kymographic records, in certain cases, will yield information about the condition of the ovaries. At the time of ovulation on the tenth to sixteenth day, the required pressure of the gas is at a maximum as is also the number and amplitude of the tubal oscillations. On the other hand, in cases of amenorrhea and at the menopause, gas goes through the tubes at a reduced pressure and the amplitude and number of oscillations are reduced.

Kymographic insufflation is superior to hysterosalpingography.

J. P. GREENHILL.

Béclère, C.: Sterility Due to Incomplete Tubal Obstruction and Its Treatment by Diathermy, Bull. Soc. d'obst. et de gynéc. 26: 453, 1937.

Since 1929 Béclère has found tubal closure in 55 per cent of the cases he has studied but the closure was incomplete in about 30 per cent of the cases. He found that after salpingography, pregnancies occurred four times more frequently in the women who had bilateral permeable tubes than among those with abnormal or diminished tubal patency.

In most cases of partial tubal closure, the cause is an attenuated chronic infection. To overcome such infections the author advocates prolonged diathermy treatment in association with vaccinothrapy. If the cervix is infected, electrocoagulation should also be employed after diathermy. Of great importance is treatment of the husband as well as the wife, otherwise reinfection may take place. Therefore, the best chances for a pregnancy are obtained by treating both mates.

J. P. GREENHILL.

Dalsace, J., and Wechsler, R. B.: Short Waves and Diathermy in the Treatment of Female Sterility, Bull. Soc. d'obst. et de gynéc. 26: 391, 1937.

In the opinion of the authors, diathermy and short wave therapy give indisputable results in the treatment of sterility. Their action on the source of infection permits to overcome tubal obstruction. The shorter the period of sterility the better the results. Hence, every attack of salpingitis should be treated as early as possible, as soon as the acute symptoms have subsided. Not only are excellent results obtained in cases of sterility by means of diathermy and short wave therapy but also these forms of treatment are followed by pregnancies in women who have dysmenorrhea, and those who have uterine and ovarian hypoplasia.

J. P. GREENHILL.

American Board of Obstetrics and Gynecology

Candidates certified by the American Board of Obstetrics and Gynecology by examination, June 13 and 14, 1938, San Francisco, Calif.

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 HAROLD CEDRIC ALWARD, Los Angeles, Calif.
 EDMUND F. ANDERSON, San Francisco, Calif.
 PHILIP H. ARNOT, San Francisco, Calif.
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 G. WILSON HUNTER, Fargo, N. D.
 GEORGE E. JUDD, Los Angeles, Calif.
 GEORGE E. KLEEMAN, JR., Oakland, Calif.
 HARVEY LEE KINCAID, Houston, Texas</p> | <p>FRANK E. KLIMAN, Los Angeles, Calif.
 LEON KROHN, Los Angeles, Calif.
 WOODBURN K. LAMB, Berkeley, Calif.
 LEONARD A. LANG, Minneapolis, Minn.
 DAVID LAZARUS, New York City, N. Y.
 FLOYD JAMES LEE, Santa Monica, Calif.
 ERNST LÖHNBERG, San Francisco, Calif.
 JEROME P. LONG, JR., Memphis, Tenn.
 WENDELL LONG, Oklahoma City, Okla.
 A. M. MCCARTHY, Los Angeles, Calif.
 A. M. MCCAUSLAND, Los Angeles, Calif.
 FRANK L. MCPHAIL, Great Falls, Mont.
 ALFRED L. MADDEN, Albany, N. Y.
 ERIC M. MATSNER, New York, N. Y.
 HERBERT L. MICHEL, Chicago, Ill.
 LEE MONROE MILES, Albuquerque, New Mexico
 DANIEL GREEN MORTON, San Francisco, Calif.
 JAMES C. MUIR, San Jose, Calif.
 MARY PETTIT, New York City, N. Y.
 WILLIAM DAVIS PHILLIPS, New Orleans, La.
 STIRLING GAINER PILLSBURY, Long Beach, Calif.
 HARRY W. PLATH, Oakland, Calif.
 WILLIAM POMERANCE, Brooklyn, N. Y.
 ABRAHAM CHARLES POSNER, New York City, N. Y.
 PHILIP A. REYNOLDS, Los Angeles, Calif.
 J. V. RIZZI, Jamaica, L. I.
 PAUL R. ROLLINS, Seattle, Wash.
 GLENN N. ROTTON, Seattle, Wash.
 KARL L. SCHAUPP, San Francisco, Calif.
 PHILIP F. SCHNEIDER, Evanston, Ill.
 MARGARET SCHULZE, San Francisco, Calif.
 FLOYD B. SHARP, Phoenix, Ariz.
 FRED BAIRD SMITH, Houston, Texas
 FRANCIS A. SNIDOW, El Paso, Texas
 RAYMOND ROSCOE SQUIER, New York City, N. Y.
 LELAND EARLE STILWELL, Hollywood, Calif.
 JAMES JAY SWENDSON, St. Paul, Minn.
 HOWARD CANNING TAYLOR, JR., New York City, N. Y.
 CURTIS HARTMAN TYRONE, New Orleans, La.
 HANS VON GELDERN, San Francisco, Calif.
 VERNON L. WARD, Ogden, Utah.
 HAROLD G. WATSON, San Francisco, Calif.
 A. N. WEBB, Los Angeles, Calif.
 PAUL W. WILLITS, Grand Rapids, Mich.
 PAUL W. WINDER, Shreveport, La.
 LEONARD WOODS, Oakland, Calif.</p> |
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This avoids injury to an early or unrecognized pregnancy. It should never be carried out in the presence of inflammatory disease or complete retrodisplacement of the uterus.

The results obtained in 150 patients in the Amsterdam clinic are reported: 47.5 per cent of women of the series became pregnant following probing; 33 per cent of women with primary sterility became pregnant, and 72 per cent of women with relative sterilities achieved pregnancy; 39 per cent of women became pregnant within six months, and 35 per cent of 115 who were sterile for more than three years became pregnant within six months.

RALPH A. REIS.

Items

Pacific Coast Society of Obstetrics and Gynecology

The next meeting of the Pacific Coast Society of Obstetrics and Gynecology will be held in Los Angeles, November 30 to December 3, 1938. Headquarters will be at the Ambassador Hotel.

Newly Elected Officers of Societies for the Current Year

NEW YORK OBSTETRICAL SOCIETY

President, Dr. Benjamin P. Watson; First Vice-President, Dr. William S. Smith; Second Vice-President, Dr. Thomas C. Peightal; Secretary, Dr. Henry T. Burns; Assistant Secretary, Dr. Ralph A. Hurd; Treasurer, Dr. William T. Kennedy.

PHILADELPHIA OBSTETRICAL SOCIETY

President, Dr. R. A. Kimbrough, Jr.; First Vice-President, Dr. Thomas B. Lee; Second Vice-President, Dr. G. A. Outerbridge; Secretary, Dr. R. W. Mohler; Treasurer, Dr. J. V. Ellson; Councillors, Dr. Norris W. Vaux, Dr. George A. Ulrich, Dr. George M. Laws, and Dr. Lewis C. Scheffey.

National Congress of Obstetrics and Gynecology

The first National Congress of Obstetrics and Gynecology will be held in Cleveland from September 11 to 15, 1939. The management is in the hands of the National Committee on Maternal Welfare, Inc., and the address of the same is 950 Rush Street, Chicago, Ill., where further information may be obtained. A tentative program is being developed which will soon be announced. There will be scientific sessions devoted to the discussion of various problems in the special domain of obstetrics and gynecology as well as in allied fields, including nursing, public health, social service, etc. A large exhibit hall will provide for both scientific and commercial exhibits.

Interested persons are urged to become members of the Congress, the fee for which is five dollars, and an active membership campaign is now under way in each state. The central office at 950 Rush Street, Chicago, Ill., will be glad to receive subscriptions. The general interest thus far manifested should assure a large attendance.

The personnel of the various committees and further news items will be published in subsequent issues of the JOURNAL.

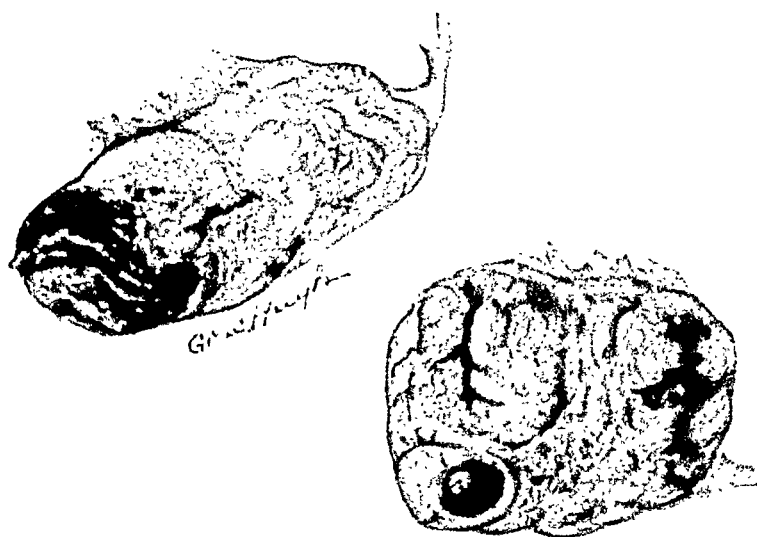


Fig. 1.—Gross-colored illustration of an ovary showing two recent ovulations. Note the hemorrhage covering the rupture site and a part of the surface of the ovary. A small amount of free blood was present in the peritoneal cavity. In addition to the ovulations present in this ovary, at least another freshly ruptured follicle was present in the ovary left in situ.

Unit Number 92689. Aged 28 years. Menstrual cycle, 24-day type. Endometrium, early proliferative. Day of cycle when hormone was administered, fourteenth. Time elapsed from the administration of hormone to removal of ovary, 38 hours. Amount of gonadotropic hormone injected, 50 units.

estrus period. Ovulation in these species is a normal periodically recurring event in the regular cycle. The second group, to which the rabbit and ferret belong, does not ovulate cyclically, as Heape has shown that in the rabbit ovulation takes place only after copulation. In the absence of the male, estrus persists through the entire breeding season and the only cycle found is estrus and anestrus. In these animals artificial stimuli simulating copulation, mechanical or electrical, likewise serve to produce ovulation.

In the rabbit ovulation normally occurs ten or twelve hours after copulation. The accurate timing of this physiologic event has enabled Allen to photograph the rupture of the follicle and the eruptive expulsion of the ripe ovum. Although nervous impulses apparently control the mechanism for the production of ovulation in this type of ovulating animals, the anterior lobe of the pituitary gland still dominates ovarian activity. Fee and Parkes have demonstrated that where the pituitary is removed within one hour after copulation, ovulation does not take place. Hypophysectomy later than one hour after copulation has no inhibitory effect on the ovulatory mechanism. Follicles which fail to ovulate undergo atresia. It must, therefore, be concluded that ovulation in the rabbit and ferret depends on two consecutive events, the first of which is nervous and the second endocrine. It can be theorized that the nervous stimulus results in the elaboration by the pituitary gland of hormones necessary to ovulation.

In 1927 Aschheim and Zondek in Germany, and Smith and Engle in this country, demonstrated by a series of experiments the dominant role of the anterior lobe of the pituitary gland in the maintenance and control of ovarian function. Thus, under the influence of the pituitary gland, follicles grow to maturity, discharge their ripe ova at periodic intervals, and their follicle cavities are converted into corpora lutea. Following hypophysectomy these accurately correlated events cease, all ovarian activity stops, and the genitalia slowly retrogress. Pituitary implants or extracts of the anterior pituitary gland cause renewed ovarian activity and complete recovery of the atrophied sex organs. Suitable implants or extracts of the anterior lobe of the pituitary can replace the function of the normal gland in hypophysectomized rats.

Following the discovery of the rich source of gonadotropic hormone in the blood and urine of pregnant women, it was thought that this substance represented the hormone of the pituitary gland itself. Experiments soon revealed that this anterior pituitary-like substance, when injected into hypophysectomized rats, failed to reproduce the action of the normal pituitary. Follicles did not grow nor did ovulation take place. The only activity exhibited by this gonadotropic substance was the luteinization of the theca cells of the follicle (Selye and his co-workers, and Leonard and Smith).

A gonadotropic substance, which differed from the substances hitherto described, was found to be present in the urine of women following a normal or artificial menopause. This gonadotropic substance, when injected into hypophysectomized rats, resulted in the stimulation of follicle growth so that numerous follicles reached ma-

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No. 2

Central Association of Obstetricians and Gynecologists

Ninth Annual Meeting, October 14 to 16, 1937

Dr. Jean P. Pratt, of Detroit, Presiding

THE EXPERIMENTAL PRODUCTION OF OVULATION IN THE HUMAN SUBJECT*†

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(From the Department of Obstetrics and Gynecology, The University of Chicago and
The Chicago Lying-in Hospital)

NORMAL reproduction is impossible without successful expulsion of the ripe ovum from its follicle. The subsequent development of the follicle into a gland of internal secretion is necessary for successful implantation of the fertilized ovum. This physiologic process is little understood in the human being for no one has actually seen a follicle rupture nor observed its ovum prior to its transport into the Fallopian tube. Mature follicles have been observed and studied and the classic work of Allen, Pratt, Newell, and Bland has revealed human ova washed from the Fallopian tube. Fortunately, many interesting facts concerning this process have been gleaned from experimental procedures on laboratory animals but gross differences are present in the various species. To cope successfully with the many problems in human reproduction, the fundamental process of ovulation must be better understood.

THE EXPERIMENTAL PRODUCTION OF OVULATION IN ANIMALS

Laboratory animals can be divided into two types as regards ovulation. The large majority of them ovulate spontaneously during the

*Presented at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

†The authors wish to acknowledge their thanks to the Upjohn Laboratories for their liberal supply of mare serum hormone and their cooperation in this work.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

stance. This substance reaches its maximum concentration about the 70th day of the animal's gestation. At no time does it appear in the urine. Chart 1 illustrates the concentration of this gonadotropic substance in relation to the period of gestation as determined by these authors. When mare serum is injected into immature animals it causes marked changes in the gonads, converting them into the mature state. It produces follicle growth, ovulation, and corpora lutea. Thus, this substance, injected in young Romanly ewes, produced ovulation during the anestrus season, and a second injection given seventeen days later resulted in a second ovulation with estrus, followed by pregnancy. Young sows could be made to ovulate, and go into estrus, and when the animals were bred, pregnancy resulted.

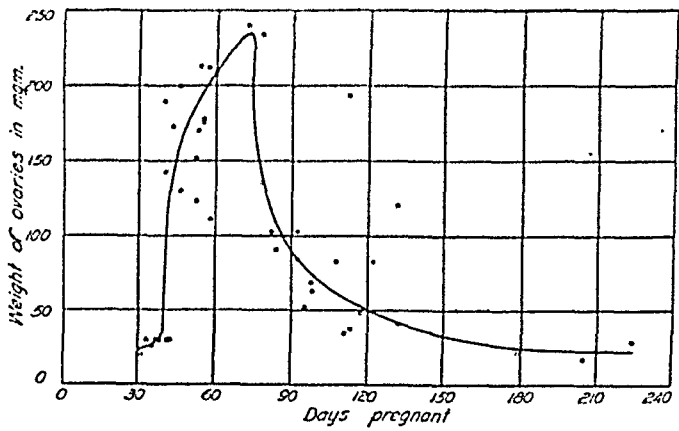


Chart 1.—Graph shows average weights of ovaries of rats injected with serum taken from mares at various stages of pregnancy. Weights include ovaries with oviducts and bursae attached. (Cole and Hart.)

These and many other experiments indicate that the gonadotropic substance present in the blood serum of the mare during pregnancy closely resembles pituitary extracts in its action. It produces follicle stimulation, ovulation and follicle luteinization. In its action it thus resembles the action of the intact pituitary (Table I).

TABLE I. REACTIONS IN OVARIES OF HYPOPHYSECTOMIZED RATS

	A.P.L. SUB- STANCE (PREGNANCY URINE)	CASTRATE OR POSTMENO- PAUSAL URINE EX- TRACTS	ANTERIOR PITUITARY EXTRACTS OR IMPLANTS	PREGNANT MARE SERUM
Follicle stimulation	-	++	+	++
Luteinization	++	-	+	+
Ovulation	-	-	+	+
Degenerative changes (hemor- rhage and atresia of fol- licles)	+	-	- +	-

Biologic studies of this gonadotropic hormone have established distinct differences between it and the other gonadotropic substances. Unlike gonadotropic substance in the blood and urine of pregnant

turity but did not ovulate. Their ova remained imprisoned, ultimately degenerated, and the follicles became atretic. Hellbaum found that the pituitary glands of horses long castrated contained only this pure principle.

It is apparent from the foregoing that the anterior lobe of the pituitary gland is responsible for two distinct reactions in the control of ovarian function. These two influences may be due to a single hormone or to two distinct fractions. Experimental evidence favors the elaboration of two discrete hormones. The first is a follicle stimulating hormone, such as that obtained from the urine of women in the postmenopausal period. Under the influence of the "follicle stimulator" primary follicles grow to maturity. The second factor is a luteinizing hormone. Ovulation and the conversion of the follicle cavity into a corpus luteum depend on the concurrent action of these two fractions at a proper stage in follicle development. A pure "luteinizer" has not been isolated as yet but the gonadotropic hormone in pregnancy urine comes the nearest to being a pure "luteinizer." Ovulation in the human being probably is the result of a proper balancing of these two actions. There is little evidence at the present to theorize the existence of an ovulation center. In the human being the entire ovulatory mechanism is under endocrinal control although in nonspontaneously ovulating animals nervous stimuli probably start the mechanism for the production of ovulation.

It has been a relatively simple procedure to produce ovulation experimentally in most laboratory animals. In nonspontaneously ovulating types ovulation can be induced by the injection of most gonadotropic principles. However, attempts to reproduce this phenomenon artificially in primates and in the human female have met with very little success. Hisaw and his co-workers have achieved this in a monkey by correctly balancing and timing the injection of follicle stimulating and luteinizing extracts. No investigators have thus far succeeded in producing ovulation in women. This is probably due to the fact that specific gonadotropic hormones have not been isolated in a sufficiently pure state. Extracts of the anterior lobe of the pituitary gland which, theoretically, should be the ideal substances have not been available in a sufficient state of purity for human therapy. Ross and Hamblen have shown that gonadotropic substances derived from pregnancy urine and blood when given parenterally have failed to produce any consistent changes in ovarian activity. One can thus conclude that the artificial production of ovulation in the human being will result only from a hormone or hormones derived from extracts of the anterior lobe of the pituitary or from gonadotropic substances simulating their actions.

GONADOTROPIC HORMONE FROM MARE SERUM

Cole and Hart, in 1930, observed that for a limited period the blood of pregnant mares contains a high concentration of a gonadotropic sub-

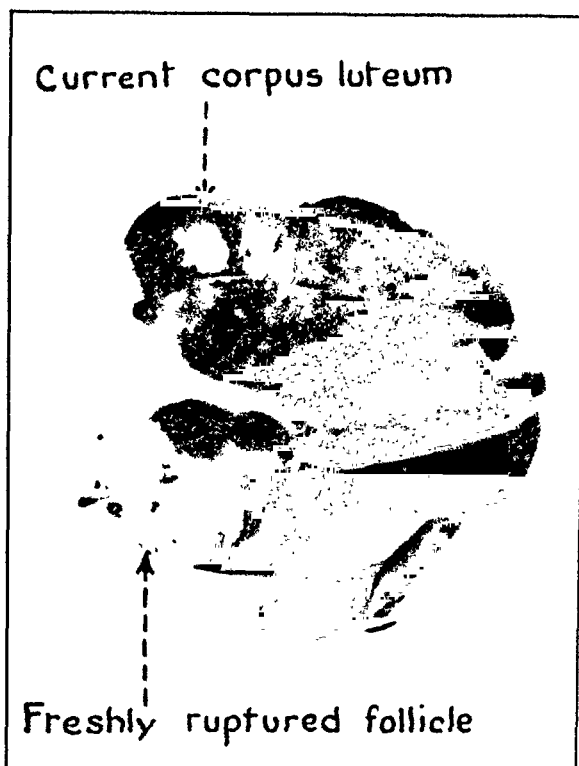


Fig. 3.—Gross view of the ovary showing recently ruptured follicle as well as the current corpus luteum (twenty-first day of menstrual cycle). Note the hemorrhagic character of the recently ruptured follicle.

Unit Number 146184. Aged 53 years. Menstrual cycle, regular 27-day type. Endometrium, late progestational type. Day of cycle when hormone was administered, twenty-first. Time elapsed from the administration of hormone to removal of ovary, 16 hours. Amount of gonadotropic hormone injected, 60 units.



Fig. 4.—Cross section through the recently ruptured follicle showing the granulosa thrown into numerous folds and marked hemorrhagic extravasation into central cavity and beneath granulosa. (Unit Number 146184.)

women, the mare serum fraction is not excreted in the urine at any time during gestation. It is not ultrafiltrable through collodion membranes as are pregnancy urine substances. Thus mare serum hormone either has a higher molecular weight or possibly is combined with a large molecule which prevents it from passing through collodion membranes. It is apparently a peptide and is not soluble in the usual fat solvents used for the isolation of estrogenic hormones.

Although it has been possible to use mare serum in experimental investigations on laboratory animals, its administration is not feasible in the human being. Cartland and Nelson have successfully obtained a highly purified preparation of this gonad-stimulating substance. Their procedure consists essentially of fractional precipitation with acetone or alcohol, removal of impurities by proper adjustment of acidity, and final precipitation of the hormone fraction in the presence

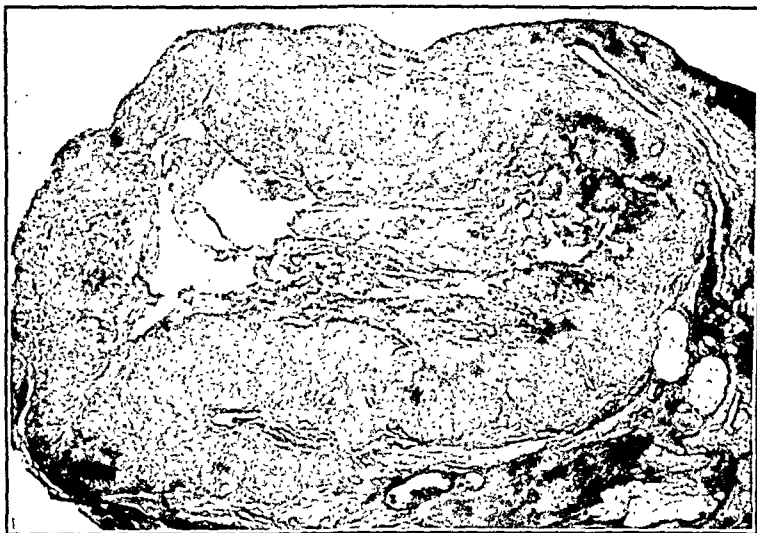


Fig. 2.—A cross section through one of the recent ovulations showing the general characteristics of a freshly ruptured follicle previously described. $\times 10$. (Unit Number 92689.)

of increased concentration of acetone or alcohol. Yields of hormone as high as 60 to 90 per cent have been regularly obtained from the crude plasma in the form of a product representing a 130-fold purification. The hormone fractions are obtained as dry, white, water-soluble powders which are remarkably stable, furnishing a satisfactory basis for preparing sterile solutions for laboratory and clinical studies. Since this preparation is unstable under ordinary conditions it must be kept in a dry state. It is essentially free of objectionable serum proteins. Many laboratory tests indicate the lack of any toxicity.

It has been biologically assayed by a method developed in the laboratories which is based upon the increased weight of the ovaries of immature female rats injected with hormone as compared with those of uninjected controls. The rat unit has been defined as the total dose of hormone which, given in divided daily subcutaneous doses in twenty-one- to twenty-three-day-old female rats weighing 30 to 40 gm., will



Fig. 6.—Gross photograph of ovary showing recent ovulation and current corpus luteum. Note the hemorrhagic character of the freshly ruptured follicle and the rupture point sealed by a gelatinous blood-tinged plug.

Unit Number 39004. Aged 31 years. Menstrual cycle, irregular. Endometrium, early proliferative. Day of cycle when hormone was administered, sixth. Time elapsed from the administration of hormone to removal of ovary, 20 hours. Amount of gonadotropic hormone injected, 50 units.

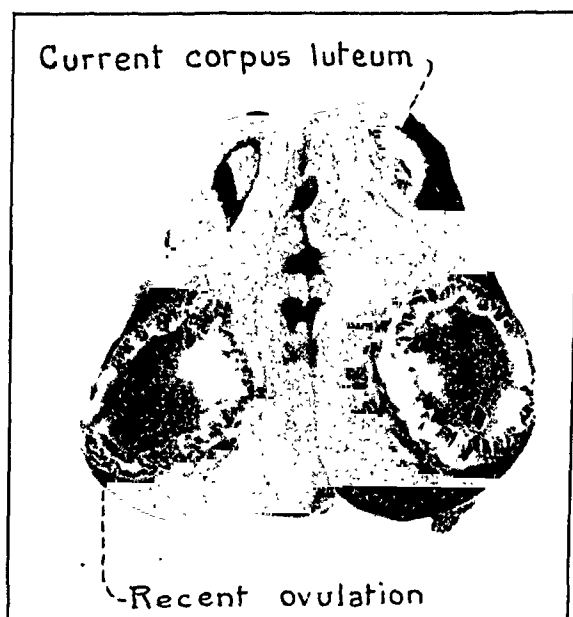


Fig. 7.—Cross section of the newly ruptured follicle showing the wavy border of granulosa cells and the follicle cavity almost completely distended by gelatinous, slightly blood-tinged fluid. (Unit Number 39004.)

produce by the fifth day a pair of ovaries weighing 65 mg., which is 5 times the weight of the ovaries in the uninjected controls. It is noteworthy that in rats the response of the ovaries varies according to the amount of hormone injected. Small doses cause maturation and ovulation of a few follicles, and little or no growth of the remaining primary follicles. On the other hand, the administration of large doses results in the development of numerous maturing follicles, luteinization of unruptured follicles, but no ovulation.

EXPERIMENTAL PRODUCTION OF OVULATION IN THE HUMAN BEING

About two years ago we became interested in the gonadotropic fraction obtained from the urine of pregnant mares, because experi-



Fig. 5.—Cross section through the current corpus luteum showing the well organized luteal border and old hemorrhage in central cavity. (Unit Number 146184.)

mental evidence indicated that this fraction was likely to produce ovulation in the human being. In our earlier experiments we administered the fraction both subcutaneously and intramuscularly with varying results. Previous experimental work indicated to us that the use of this substance was likely to be most successful when administered intravenously. The available patients were carefully tested for protein sensitization, and the hormone was then administered intravenously. Women who were to be subjected to laparotomy for a variety of pathologic conditions were chosen for this work. Many of our subjects were at the period in life when there is a rapid decrease

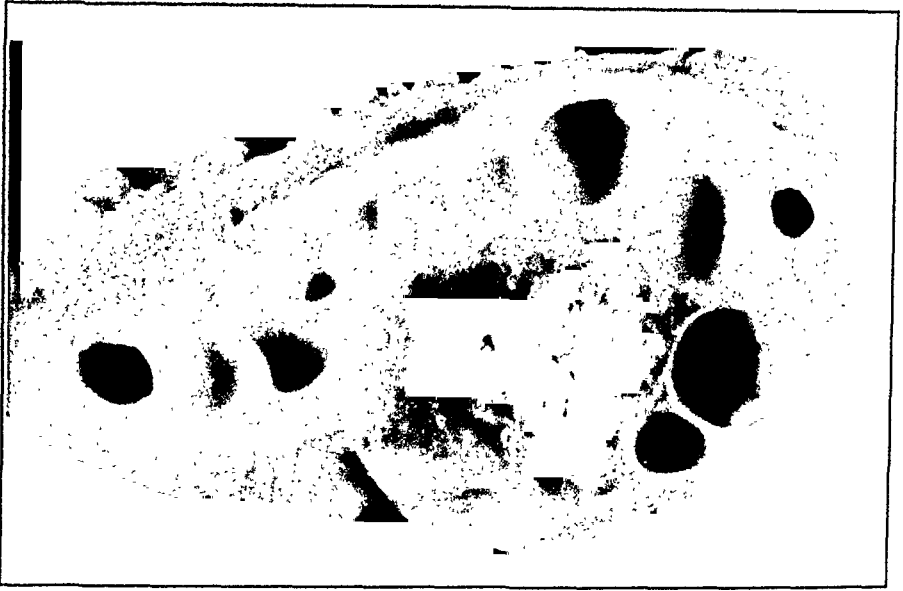


Fig. 10.—Gross view of ovary containing recent ovulation. The follicle walls were almost completely collapsed so that the folds were numerous. The small cavity contained a small amount of hemorrhagic fluid. The entire follicle presented a reddish, hemorrhagic appearance.

Unit Number 26755. Aged 38 years. Menstrual cycle, irregular. Endometrium, menstrual phase. Day of cycle when hormone was administered, seventh. Time elapsed from the administration of hormone to removal of ovary, 22 hours. Amount of gonadotropic hormone injected, 60 units.



Fig. 11.—A higher magnification of a portion of the corpus luteum showing the relatively unaltered appearance of the granulosa cells and the marked vascularity and congestion of the surrounding ovarian stroma and the theca interna. $\times 65$. (Unit Number 26755.)

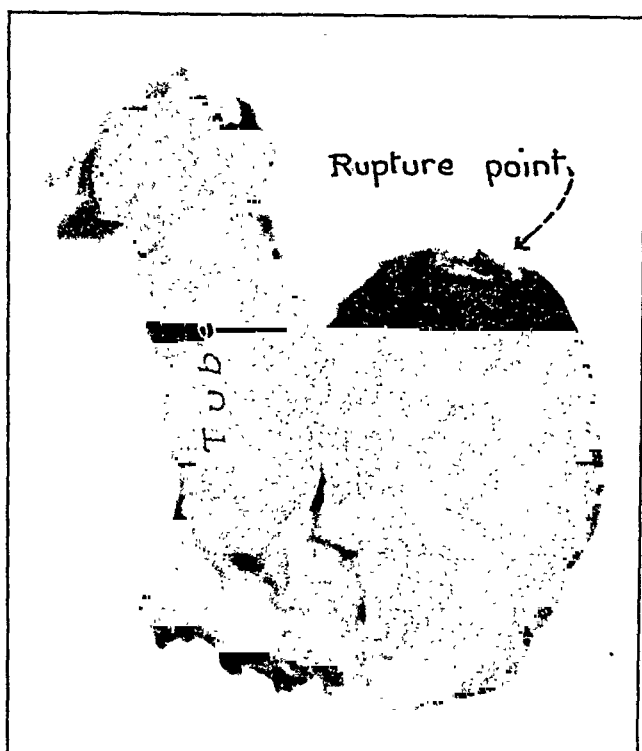


Fig. 8.—Gross view of one of the recent ovulations showing the site of rupture of the follicle. Close inspection of this fresh rupture point showed a pinkish-gelatinous fluid exuding from it.

Unit Number 64164. Aged 22 years. Menstrual cycle, 14- to 21-day type. Day of cycle when hormone was administered, fifteenth. Time elapsed from the administration of hormone to removal of ovary, 17 hours. Amount of gonadotropic hormone injected, 60 units. Ovaries showed two recent ovulations and current corpus luteum.

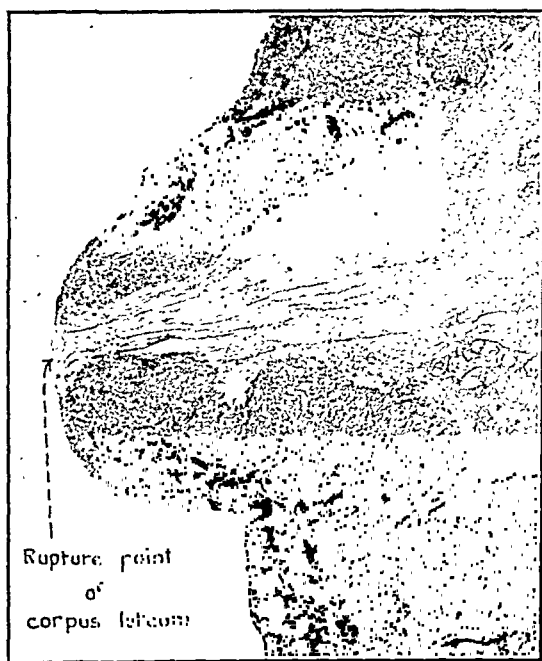


Fig. 9.—A cut section through this rupture point showed the cavity partially filled with a bloody fluid. Histologic examination revealed no luteal transformation. No fibroblasts had migrated through the granulosa layer. (Unit Number 64164.)

TABLE II. RÉSUMÉ OF FINDINGS IN A GROUP OF PATIENTS WHO RECEIVED MARE SERUM HORMONE

	AGE	MENSES			NO. OF UNITS OF UNITS	HOURS ELAPSED	NO. OF OVULA-TIONS	CORPORA LUTEA		MATURE FOLLICLES	ATRETIC FOLLICLES	ENDOMETRIUM
		INTERVAL	INJEC. DAY OF CYCLE	NEW				OLD				
1	44	IR.	2	60	18	1	1		++		Early proliferative	
2	47	21	2	50	22	1		1		++	++	Early proliferative
3	37	28	3	60	16				++	+	+	Early proliferative
4	28	22-24	3	60	15	1		1		+		None
5	37	33	5	70	40							Early progestational
6	31	IR.	6	50	20	1	1	1	+			Early proliferative
7	42	28	7	60	65	1	1					Early proliferative
8	40	30	7	60	40	2	1	1				Late proliferative
9	38	IR.	7	60	23	2						Late menstrual
10	35	25	9	60	17				++			None
11	44	28	11	50	23	3	2	1	++			Early proliferative
12	45	28	11	60	17	1		1	++	++	++	Early proliferative
13	30	28	12	60	18	1			++	+	+	Late proliferative
14	42	27	13	60	22				++		+	Glandular hyperplasia
15	37	25-33	13	50	13	1		1	++			Glandular hyperplasia
16	39	23	14	60	42				++			Progestational
17	28	24	14	50	38	3	3		++			Early proliferative
18	41	24	15	60	42	1	2	1	++			None
19	22	14-21	15	60	17							None
20	36	28-31	16	90	76	2	1	1				None
21	43	28	16	60	24	1		1	++			None
22	39	28	21	60	22	1		1	++	++	++	Early progestational
23	33	27	21	60	16	2	1	1	++			Progestational
24	37	28-31	22	60	22	2			+			Late progestational
25	27	28	22	60	23	2	1	1				Progestational
26	38	28	22	60	16	1		1				None
27	40	28	23	60	45	1		1	++	+	+	Early progestational
28	32	24	25	60	20	1		1	++	+	+	Late progestational
29	37	28	26	60	10	1		1				Progestational
30	47	IR.	27	60	15							Late progestational
31	42	28	28	60	32	3	1	2	++		++	Glandular hyperplasia
32	46	Metrorrhagia	28	60	15	1			++			Late progestational
33	30	Metrorrhagia	Metrorrhagia	60	38	2	1	1	++		++	Glandular hyperplasia
34	46	Metrorrhagia	Metrorrhagia	60	38	2	1	1	++			Late progestational
35	31	28-30	18	50	64	3	1	1				Inactive
36	37	IR.	18	60	16	1	3					Proliferative
				60	18	1		Stigma				Late proliferative

of ovarian activity. Others had pathologic conditions which would mask any results which might be obtained. However, it was absolutely necessary to examine the ovaries in situ and to subject them to careful histologic study to determine the effectiveness of the preparation as judged by the reactions induced in the ovaries. The time interval from the administration of the substance to the time when the ovaries were inspected and removed was varied. Evidence concerning the reactions of the ovaries to the substance at different times in the ovarian cycle was likewise accumulated. Table II presents a résumé of the patients who received mare serum gonadotropic substance.

DISCUSSION

From the foregoing table and illustrations it is evident that recent ovulation was present in approximately half of the patients to whom

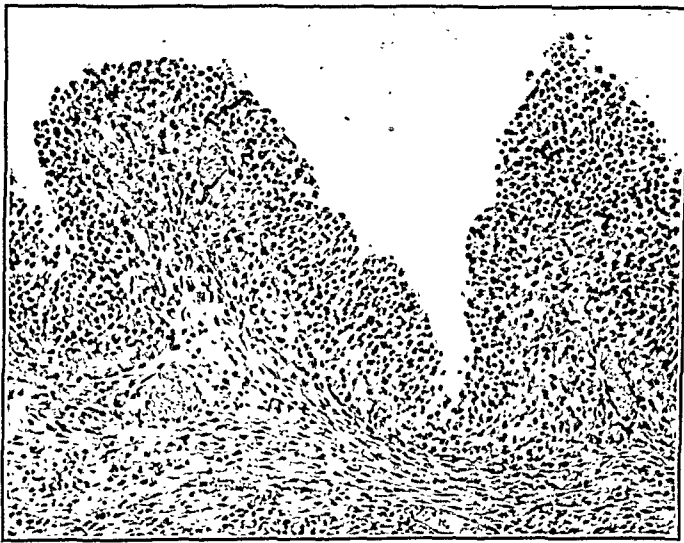


Fig. 12.—A section of the wall of the recently ruptured follicle showing the early proliferation of the granulosa cells. They still retain the follicular characteristics showing no luteal transformation. No fibroblasts have migrated into the cavity from the theca interna. Groups of theca interna cells stand out rather prominently. $\times 180$.

Unit Number 162189. Aged 45 years. Menstrual cycle, 28-day type. Endometrium, early proliferative phase. Day of cycle when hormone was administered, eleventh. Time elapsed from the administration of hormone to removal of ovary, 17 hours. Amount of gonadotropic hormone injected, 60 units.

this substance was administered. To make certain that an ovulation is of recent origin, it is almost always necessary to obtain histologic sections of the corpus luteum. It is difficult to estimate the age of a ruptured follicle by gross inspection alone. In many instances the current corpus luteum which represented the patient's normal follicle activity was present in addition to the recent corpus luteum. This was additional evidence that the recently ruptured follicle was artificially produced by the gonadotropic substance. Furthermore, in a number of instances more than one corpus luteum of recent origin was present, thus suggesting that more than one follicle can be made to ovulate by administering adequate amounts of this substance.

subcutaneously or intravenously. On the other hand, he was able to induce ovulation in these animals by a single intravenous administration of a large amount of hormone.

The duration of time that elapsed from the administration of the substance until ovulation was produced was unusually short. We have

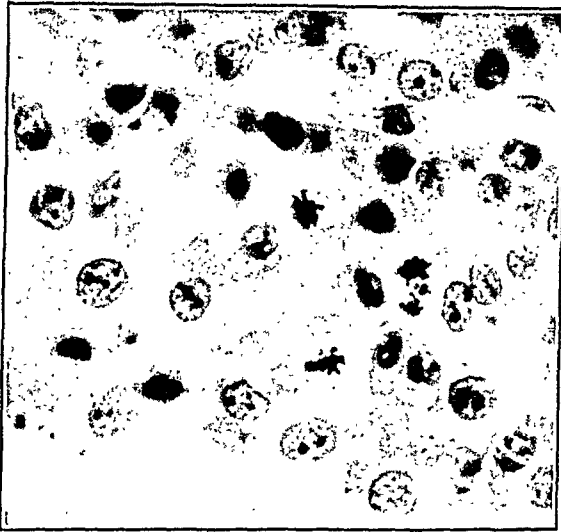


Fig. 13.—The wall of a large unruptured follicle showing the active proliferation of the granulosa as a result of the administration of gonadotropic hormone. Note the numerous mitotic figures.

Unit Number 154313. Aged 44 years. Menstrual cycle, regular 28-day type. Endometrium, early proliferative phase. Day of cycle when hormone was administered, eleventh. Time elapsed from the administration of hormone to removal of ovary, 23 hours. Amount of gonadotropic hormone injected, 50 units.



Fig. 14.—The granulosa cells appear as in the mature follicle prior to its rupture. Theca interna cells can be seen in the folds between the granulosa border. $\times 140$. (Unit Number 154313.)

been led to believe that the process of ovulation in the human being extends over a period of several days or longer during which time the follicle slowly reaches maturity and ultimately, some time in the mid cycle, ruptures and discharges its ripe ovum. It is probable that in many of our experiments maturing follicles were already present, so

In evaluating the effect of gonadotropic hormone it was necessary to establish the exact age of the corpora lutea present in the ovaries. Gross and histologic studies of our material revealed earlier stages in the formation of the corpora lutea than heretofore published. The best collections of early corpora lutea rather accurately dated are those described by Allen, Pratt, Newell, and Bland. Their criteria of age were followed.

Grossly, the majority of these corpora lutea showed distinct points of rupture, either hemorrhagic in character or exuding a bloody fluid, or a blood-tinged gelatinous substance. In only two follicles were there distinct plugs and a distention of their cavities by a blood-tinged gel. A slight amount of blood-tinged fluid was present in most of the follicle cavities.

Histologic examination revealed the walls of the follicles collapsed and greatly folded. In most instances the granulosa cells of the follicle seemed little altered from the prerupture stage. No apparent luteinoid changes could be discerned. In several instances the early stage of luteal hypertrophy was present. The "streaming out" effect of the coagulum suggestive of secretory activity on the part of the granulosa was present in the majority of the corpora lutea. There was no migration of fibroblasts into the granulosa layer or evidence of vascularization. A careful comparison of these corpora lutea with those described by Allen and his co-workers indicates that the majority of our corpora lutea were less than eighteen hours old and few as old as thirty-six hours. Their age was well within the period of time which elapsed between the administration of the gonadotropic hormone and the time of the removal of the ovary in question.

In the illustrations the gross and microscopic characteristics of a few of these early corpora lutea are pictured. A comprehensive study on the development of the human corpus luteum will be published at a later date.

The endometrium was obtained and studied in most of the cases. It was impossible to correlate the stage of endometrial development with the menstrual data in many instances, for all of these patients presented pathologic changes of the genital organs necessitating the pelvic surgery. Furthermore, irregular bleeding was the outstanding symptom in many of the patients.

Although most of our patients received about 60 units in a single dose, the results obtained by using the larger doses have not been determined as yet. In experimental animals it has been found that large doses of mare serum are likely to produce unusual enlargement of the ovaries without corpora lutea. Thus, the dosage required for excessive enlargement is much greater than that required to produce ovulation. We believe that it has been possible to provide the necessary impulse for ovulation in these patients by the intravenous administration of this gonadotropic hormone principle. Snyder has shown that early in pregnancy the ovaries of rabbits do not respond to small amounts of gonadotropic hormone repeatedly administered

The clinical application of this experimental work presents certain problems. The majority of the group of patients used in this work were probably having normal ovarian activity and periodic ovulations. To produce artificial ovulation in women with normal ovaries may be less difficult than to do so in women who have little or no ovarian activity. The therapy of this new gonadotropic material involves the treatment of patients in whom ovarian failure has resulted in a lack of follicle development and an absence of normal ovulation with their concomitant menstrual abnormalities or infertility. In these women the dosage of the hormone, the interval, and the method of its administration will determine to a large measure the success of the therapy.

Much laboratory experimentation indicates that the amount of hormone sufficient to stimulate growth of follicles may not be sufficient to produce ovulation. Too large an amount of gonadotropic substance causes the formation of many atretic follicles and the imprisonment of their ova but no ovulation. We have some clinical evidence that the most effective mode of administration is to give two or three intramuscular injections of 15 or 20 units at daily intervals to be followed by a single intravenous administration of the same or a larger amount. Thus, follicles can be stimulated to grow to maturity at which stage the intravenous administration provides the stimulus necessary to cause ovulation. These and many other problems will have to be worked out by prolonged clinical investigation.

In general, clinical administrations of gonadotropic substances have met with very little therapeutic success. Most of them have not been isolated in a sufficiently pure form so that they can be used in the human being. Those that have been purified to this extent have been ineffective in the production of changes in the ovaries. The reports of the successful use of some of these gonadotropic substances have been based on casual observations and have not been substantiated by careful workers. Ross and Hamblen, in a recent report, concluded that gonadotropic substances are not available in sufficient concentration to provide desirable therapeutic results.

Judging from the results of these investigators, substance from pregnancy urine will probably find little place in therapy. The source of hypophyseal glandular extracts is obviously limited. On the other hand, mare serum provides a concentrated and abundant source for a gonadotropic substance which apparently stimulates normal physiologic changes. It will be necessary to do a great deal more work to determine just how this substance fits into our glandular therapeutic armamentarium.

CONCLUSIONS

1. It has been possible for the first time to produce ovulation in women by the intravenous use of a gonadotropic hormone derived from serum of pregnant mares.

that completion of the process resulting in ovulation was very rapid. On the other hand, in the women who were in the latter half of the cycle, maturing follicles ordinarily should not have been present, and yet we found recent ovulations with equal frequency during this period. We can thus theorize that this substance is capable of causing rapid follicle growth, and that these follicles rupture, release their ova and are converted into corpora lutea all within the space of twenty-four to thirty-six hours. Experimental evidence lends weight to this theory. For example, the rabbit normally ovulates about ten hours after copulation, or after the administration of a suitable gonadotropic substance.



Fig. 15.—The coagulated substance extending from the granulosa cells has been described as a "streaming-out" phenomenon. The individual granulosa cells show no evidence of luteinization. No fibroblasts have penetrated into the cavity. $\times 525$. (Unit Number 154313.)

It should be noted from Table II that the majority of recent ovulations were found in women between the fifth and thirteenth day, and between the seventeenth and the twenty-fifth day of their cycles. In some of these women it was impossible to date the cycle. The significance of this fact is as yet not understood. It should also be noted that in three women who had metrorrhagia and no definite rhythm to their bleeding, ovulations were present in all. This fact is of importance in that it may point the way to a clinical use for this substance. However, in three cases among this series where the endometrium showed typical glandular hyperplasia, no ovulations occurred. The significance of these observations is not yet clear.

A STUDY OF THE WATER, SODIUM, AND ENERGY EXCHANGE DURING THE LATTER PART OF PREGNANCY*

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IT HAS been suggested that retention of water may be the cause of the toxemias which occur late in pregnancy (pre-eclampsia and eclampsia). Cummings¹ found that the incidence of toxemia was greater in those patients who gained more than thirty pounds during pregnancy. He further pointed out that rapid and excessive gains in weight during the eighth and ninth months were the results of fluid retention, and appeared several weeks before definite edema could be demonstrated. Wieloch² states that water retention occurs universally in his cases of toxemia of pregnancy. Arnold and Fay³ have reported the prevention and control of eclampsia by restricting the fluid intake to the amount of urine the patient excretes and by further dehydrating the patient by the use of magnesium sulphate and hypertonic solutions of dextrose.

It is well known that water is often retained in cases of toxemia of pregnancy in amounts sufficient to cause gross edema. Indeed, the opinion is quite prevalent that not only in cases of toxemia, but in *all* pregnant women water is retained in excess of the amount needed to form the fetus and its adnexa and the new maternal protoplasm. Fink⁴ claims that in 95 per cent of his cases of pregnancy there is some degree of "occult or gross edema." Stander⁵ and more recently Oberst and Plass⁶ have shown that there is an increase in blood volume and a dilution of the blood during pregnancy.

From observations such as these it is apparent that a knowledge of water metabolism during pregnancy is needed. Except for studies of the blood, all approaches to the study of water metabolism during pregnancy have been entirely inadequate. Recently, as a result of the researches of Newburgh and his associates^{7, 8} and Peters,⁹ it has been possible to deal directly with the problem of water metabolism.

We have started investigations planned to throw more light on the problems of water metabolism during pregnancy and the suggested disturbance of water balance associated with the toxemias. The first study, reported herein, concerns primarily the exchange of water and sodium during the last two months of normal pregnancy and a short period post partum. Data regarding the exchange of nitrogen and total energy, obtained during the course of this investigation, are included in this communication.

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2. This hormone has been isolated in such an advanced state of purity that its administration by the intramuscular or intravenous route is devoid of danger, provided that suitable safeguards are established.

3. Biologically, this gonadotropic hormone resembles extracts and implants of the anterior lobe of the hypophysis but differs chemically and biologically from all other gonadotropic substances heretofore studied.

4. These experimental ovulations have provided the earliest human corpora lutea yet described.

5. Clinically, this gonadotropic hormone should prove efficacious in the therapy of patients in whom follicle growth and ovulation are at fault.

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The author reports on 27 fibroadenomas removed during pregnancy and lactation, or present during that period and removed at varying intervals following the cessation of lactation. It was observed that the tumors were modified by pregnancy and lactation, and that the changes produced in them were similar to those occurring simultaneously in the surrounding normal breast tissue, probably are of hormonal origin.

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study the patient cooperated splendidly; she ate all of the food each day except on the day of delivery and two days early in post partum. Vomiting, proteinuria, and glycosuria never occurred, hence the intakes and the urinary and fecal excretions of the substances studied were satisfactorily determined.

Details of the water balance and the net balance of sodium, nitrogen, and energy, and the body weight are presented in Table I. In Chart 1 the body weight and the exchange of nitrogen, energy, sodium, and water are shown graphically.

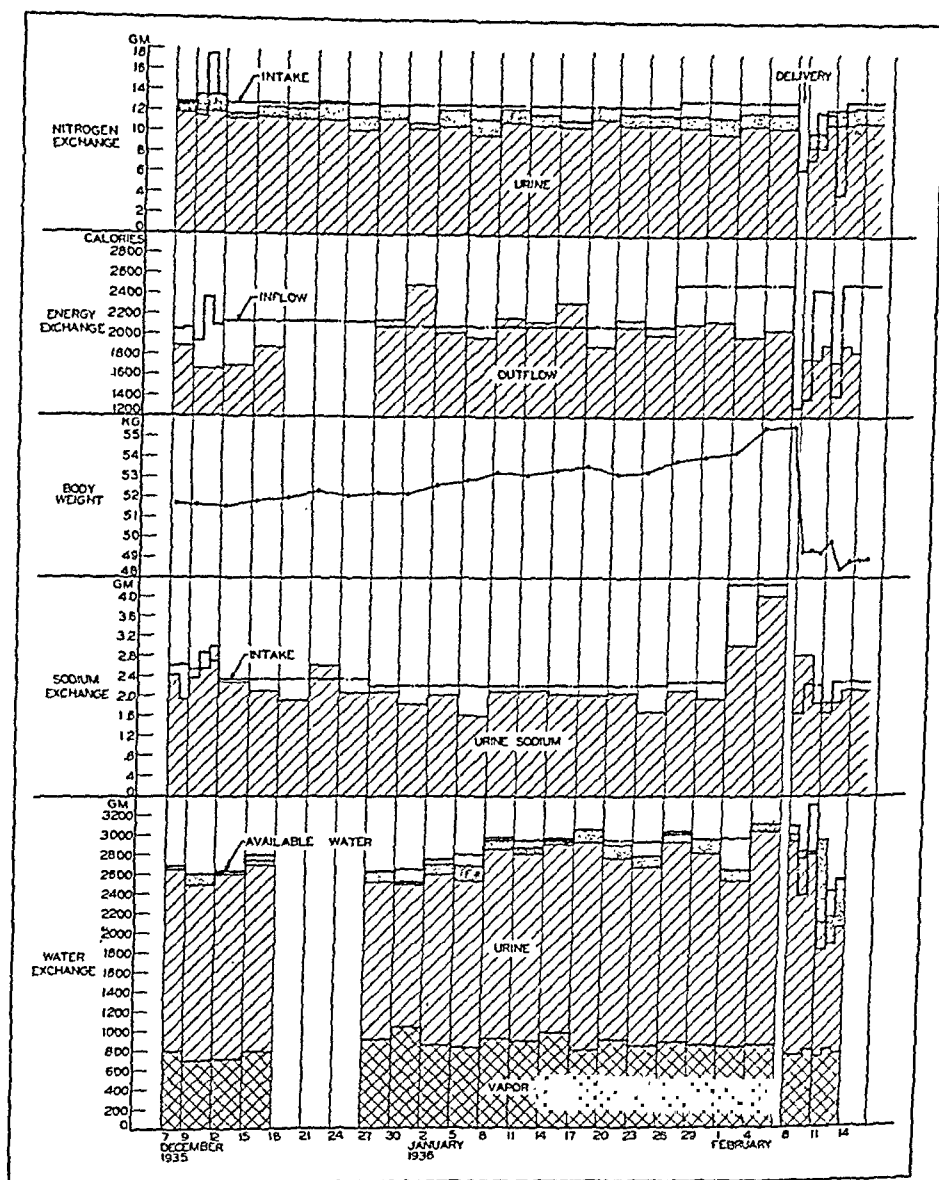


Chart 1.—The nitrogen, energy, sodium, and water exchange and body weight during the last two months of pregnancy and early post partum. *F*, in each case represents fecal excretion.

From December 18 through December 26, because of improper regulation of the room temperature, sweating, crying spells, and an acute upper respiratory infection, insensible loss of weight could not be accurately determined. As a result water and energy exchange could not be calculated during this time. On the day of delivery due to sweating and other unusual events, it was impossible to make the usual observations. In Table II the items accounting for the reduction in body weight (6,256 gm.) on the day of delivery are presented.

METHOD

The subject of this study was an American girl, aged 17 years, who was in her first pregnancy. She was 157.5 cm. in height. Her average pregravid weight was 46.5 kg. She had been in splendid health before this pregnancy. During the second and third months she had only slight nausea and occasionally vomited, otherwise she felt entirely well throughout the pregnancy.

Beginning on the seventieth day before delivery she was fed a simple weighed diet consisting of milk, eggs (boiled), bread, butter, jelly, corn flakes, canned pears and grapefruit, and sugar. The diet was identical day after day. It contained 82 gm. protein, 91 gm. fat, and 247 gm. of carbohydrate; the calorific value was 2,133 or about 46 calories per kg. of pregravid body weight. There was an excess of alkaline ash equivalent to approximately 12 c.c. normal alkali.

On December 27 (at the end of four weeks) the diet was changed slightly; salmon was substituted for the eggs, and different fruit was served. The dietary formula, however, was practically unchanged: protein 82 gm., fat 93 gm., carbohydrate 230 gm., calories 2,085. This diet was served daily until January 26, when it was changed by the addition of 110 gm. of 40 per cent cream, altering its composition to protein 85 gm., fat 137 gm., carbohydrate 233 gm., calories 2,498. Beginning February 6, jelly was omitted and the amount of butter was increased to keep the calorific value the same. This was the last change made in the diet.

Metabolism studies were begun on the sixty-second day before delivery and continued throughout the remainder of pregnancy and for a short period in puerperium. During most of the time the metabolism periods consisted of seventy-two hours; for a short time at the beginning and post partum, twenty-four hourly periods were employed. Heat production was determined by the method of Newburgh, Wiley and Lashmet,¹⁰ which depends on the measurement of insensible loss of weight. The *actual* percentage of total heat eliminated by the vaporization of water was determined* in the manner described by Newburgh and others,¹¹ and this factor was used in calculating total heat production from insensible loss of water. Since the patient was quantitatively fed, energy balance could be calculated. Nitrogen balance was determined by analysis of ingesta and the urine and feces by the Kjeldahl method. One tenth gram was added to the measured, daily nitrogen excretion, to represent the nitrogen loss from the skin and its appendages.

Complete water balance was determined according to the technique of Wiley and Newburgh.⁸ This method deals with all the known increments of water exchange: as sources of water the water of food, water drunk, water resulting from the oxidation of foods, and preformed water are determined, and the amounts of water eliminated in the urine and stool, and as vapor are measured separately.

Sodium balance was calculated by comparison of the intake and the urinary excretion of this element. The amount of sodium in the ingesta and urine was determined by the Butler-Tuthill¹² method. Wiley and Wiley¹³ have shown that the fecal excretion of sodium is negligible. Sodium eliminated through the skin was ignored in this study. To increase the sodium intake 5 gm. of NaCl were fed daily, in capsules, from February 1 through February 6.

There was no lactation post partum. The water of the lochial discharge was included along with fecal water in the considerations of water exchange post partum.

RESULTS

The entire course of pregnancy was normal in every respect. The total gain in weight was very close to 9 kg. During the last two months there was a gain of 3,793 gm. Visible edema was never present. The pregnancy ended at full term by the spontaneous delivery of a healthy male baby weighing 3,229 gm. Throughout the

*Drs. L. H. Newburgh, M. W. Johnston, and J. M. Sheldon made this determination.

DISCUSSION

Chart 1 shows the nitrogen retention during this study. Throughout the last sixty-two days of pregnancy, 50.8 gm. of nitrogen were retained; the average daily retention was 0.82 gm. This is distinctly less than was found by Hunscher and others¹⁴ in their own investigation (3.1 gm. daily), and less than that observed (2.28 gm. daily) by other investigators as reported by Hunscher¹⁵ in a review of the literature. The reason for the difference is undoubtedly the result of a number of factors including the size, state of nutrition, and physical activity of the mothers prior to pregnancy, the size of the babies, and the nitrogen and calorific values of the diets. For instance, Hunscher's patient was 68.5 inches tall and normally weighed 135 pounds, in contrast to the smaller size of our subject. Moreover, Hunscher's subject received an average of 19 gm. nitrogen and 3,400 calories daily in contrast to 13 gm. nitrogen and about 2,200 calories fed our subject. The protein in our diet was of good biologic value, and the amount of nitrogen retained was more than sufficient for the formation of a fully developed fetus and its adnexa.¹⁶ It should be noted that from January 26 until delivery on February 7, when the calorific value of the diet was greater than previously, the nitrogen retention was also slightly greater. During early post partum, the nitrogen exchange was irregular; later there was a slight retention of nitrogen.

TABLE II. KNOWN ITEMS OF WEIGHT LOSS DURING THE DAY OF DELIVERY

	GRAMS
Baby	3,229
Placenta, cord, and membranes	433
Amniotic fluid	354
Blood	124
Vaginal discharge	105
Urine	1,401
Feces	440

A study of the energy exchange reveals several interesting facts. From December 7 through December 17, the energy inflow exceeded the energy outflow by 3,820 calories, an average of 347 calories daily. Since the water exchange during this period was slightly negative, the increase in weight (304 gm.) recorded during this time resulted from the formation of new protoplasm. A simple calculation will prove that this statement is true. Assuming that the amount of glycogen in the body remains constant and that true water balance exists, changes in body weight will be the result, almost entirely, of changes in the amount of protein and fat in the body. From December 7 through December 17, 5.95 gm. of nitrogen were retained. This represents 37 gm. dry protein ($N \times 6.25$) which will require the association of 111 gm. water (3 gm. of water per 1 gm. dry protein). This 37 gm. of protein accounts for the storage of 148 calories. Since the energy exchange shows a retention of 3,820 calories during this period, 3,820 minus 148, or 3,672 calories must have been stored as fat. The weight of the fat stored is 3,672 divided by 9.54 or 383 gm. With this amount of fat, 38 gm. of water are stored (0.1 gm. water per 1 gm. fat). The body weight during this period should be increased by the sum of these items (37 plus 111 plus 383 plus 38) or 569 gm. if water balance obtained. However, during this period, the elimination of water exceeded the intake by 283 gm., hence, the net gain in weight would be 569 minus 283, or 286, which very closely approximates the observed increase in body weight, 304 gm. The small difference is readily understood when one considers the deposition of inorganic material and glycogen in the growing fetus, which has been ignored in this calculation.

From December 27 through January 25, the energy transformation exceeded the inflow by 1,510 calories, 50 calories daily. During this same period there was a retention of 1,399 gm. of water in excess of that used in the formation of new protoplasm. This accounts for most of the increase in weight (1,532 gm.) observed during this period. Because of the slightly negative energy balance beginning January 26 the calorific value of the diet was increased by 415 calories daily, making the

TABLE I. DETAILS OF THE WATER EXCHANGE, AND SUMMARY OF THE SODIUM, NITROGEN AND ENERGY EXCHANGE

DATE	WATER EXCHANGE										SODIUM BAL-ANCE GM.	NITRO-GEN BAL-ANCE GM.	ENERGY BAL-ANCE CAL.	BODY WEIGHT AT END OF PERIOD GM.
	WATER OF FOOD GM.	WATER DRUNK GM.	WATER OF OXIDA-TION GM.	PRE-FORMED WATER GM.	TOTAL AVAIL-ABLE WATER GM.	WATER OF URINE GM.	WATER OF FECES GM.	WATER VAPOR GM.	TOTAL WATER ELIM-INATED GM.	WATER BAL-ANCE GM.				
Dec. 7, 8	2995	1802	493	5	5295	3696	77	1596	5369	- 74	0.91	-0.37	331	51,642
9-11	4927	1936	659	-53	7469	5375	318	2097	7790	-330	0.25	2.08	1434	51,573
12-14	4819	2486	658	-74	7889	5684	32	2149	7865	24	0.22	3.27	1306	51,509
15-17	4853	2803	757	-23	8390	5731	178	2384	8293	97	0.71	0.97	749	51,796
18-20	4841	2768	*	*	*	4311	421	*	*	*	1.32	1.33	*	51,946
21-23	4856	2894	*	*	*	5000	355	*	*	*	-0.79	-0.38	*	52,331
24-26	4834	2904	*	*	*	3733	295	*	*	*	0.88	3.97	*	52,064
27-29	5049	2020	822	- 2	7889	4839	270	2732	7841	48	0.36	0.19	-235	52,220
Dec. 30-Jan. 1	5062	2071	936	-90	7979	4340	88	3157	7585	394	1.13	5.48	-1242	52,213
Jan. 2-4	5074	2472	778	-32	8292	5216	314	2565	8095	197	0.54	1.63	161	52,600
5- 7	5061	2668	761	-78	8412	5092	460	2497	8049	363	1.82	4.06	322	52,809
8-10	5067	2986	827	-19	8861	5840	348	2750	8938	- 77	0.32	1.18	-277	53,251
11-13	5077	3002	811	-47	8843	5720	208	2693	8621	222	0.28	2.60	-142	53,146
14-16	5074	3038	877	-75	8915	5762	111	2945	8818	97	0.55	4.44	-740	53,387
17-19	5080	2968	728	- 6	8770	6370	430	2389	9189	-419	0.62	0.01	578	53,505
20-22	5065	2999	817	-42	8839	5588	387	2716	8691	148	0.55	2.36	-197	53,092
23-25	5073	2991	761	-54	8771	5513	311	2521	8345	426	1.64	2.80	265	53,243
26-28	5260	3053	803	-87	9029	6102	330	2659	9091	- 68	0.43	4.06	1193	53,752
29-31	5243	2970	780	-102	8891	5851	460	2562	8873	18	0.95	4.77	1422	53,902
Feb. 1-3	5212	3015	751	-73	8905	5089	321	2494	7904	1001	3.65	3.10	1584	54,143
4-6	5198	3226	771	-74	9121	6508	241	2573	9322	-201	0.78	3.26	1396	55,395
7	870	141	*	*	*	†	512	*	*	*	†	†	*	55,435
8, 9	2937	2084	447	11	5479	4216	137	1483	5836	-357	-1.80	-0.61	280	49,179
10	1722	1344	241	1	3308	1999	26	798	2823	485	0.36	-0.41	542	49,158
11	965	493	211	160	1829	1380	858	723	2961	-1132	-0.16	-8.37	-329	49,725
12	1745	457	240	-22	2420	1090	278	792	2160	260	0.46	0.85	621	48,251
13	1741	598	232	-18	2553	1279	483	763	2525	28	0.18	0.60	690	48,591
														48,704

*Water vapor could not be accurately determined.

†Amniotic fluid mixed with part of urine on this day.

the disposition of water during normal pregnancy. After this subtraction is made (1,881 minus 1001) 880 gm. of water remain.

To understand where this water is located, one must consider many possibilities. The amount of amniotic fluid might be increased. Beck,²⁰ however, states that commonly there is no increase in amniotic fluid after the seventh month, in fact it usually decreased in amount.

It is well known that maternal blood volume usually increases during pregnancy.⁵ In our subject the volumes of maternal blood and plasma were measured* at intervals (during the last two months of pregnancy) and were found to be:

DATE	PLASMA VOLUME	TOTAL BLOOD
	C.C.	VOLUME C.C.
Dec. 7, 1935	2,340	4,140
Dec. 27, 1935	2,380	4,100
Jan. 17, 1936	2,400	4,210
Feb. 7, 1936 (early in labor)	2,160	3,660

From these data we cannot ascribe any of the retained water to the maternal blood.

The weight of the fetus normally is doubled during the last two months of intra-uterine life. Accordingly it is reasonable that the fetus in our subject added at least 1,500 gm. to its mass during the period of study. Since the water content of the normal human fetus at full term is approximately 70 per cent of its weight, it can be estimated that 1,050 gm. of water were added to the fetus during the period of investigation. Of the total amount of water used in the formation of new protein and fat (931 gm.), the portion entering into the formation of *fetal* tissue cannot be directly determined. However, Macy and Hunscher¹⁶ state that during the last two lunar months of pregnancy an average of 43 gm. of nitrogen are retained by the human fetus. Assuming the fetus in our subject added this amount of nitrogen to its mass, then 806 gm. water were added along with it. Accordingly, 244 gm. of water (1050 minus 806) were added to the fetus in excess of that united with the protein made. Thus, it is reasonable, ignoring the small amount of water stored with fat tissue (0.1 gm. water per 1 gm. fat) that no more than 636 gm. of water (880 minus 244) were retained by the *maternal* organism throughout this last two months of pregnancy, in excess of that amount used in formation of new tissue ("superhydration"). This amount of water retained is only 1.3 per cent of the immediate postpartum body weight, and averages 12 gm. daily. Since fluctuations of 500 gm. of body water are common, and a gain or loss, up to 1,000 gm., has been observed²¹ in a normal male individual when the intake of food and water, and the physical activity, were constant, we do not consider the retention of 634 gm. of water by our subject significant of an important "superhydration."

SUMMARY AND CONCLUSIONS

The nitrogen, energy, sodium, and water exchanges observed during the last two months of normal pregnancy, and for a short period post partum, are presented. Changes in body weight are discussed in relation to the energy, sodium, and water balance. The larger fluctuations in body weight resulted from significant changes in the body water, which accompanied parallel shifts in sodium balance. When the intake of sodium was abruptly increased by feeding 5 gm. of sodium chloride daily for six days, there was a marked retention of sodium and water during the first three days; the sodium and water balance were negative during the first few days after the sodium in-

*Blood volume determinations were made by Dr. F. H. Bethell.

energy balance again positive. This accounts for the gain in weight (391 gm.) during the following six days when there was almost exact water balance.

Following parturition the energy transformation lessened due to the confinement to bed, and to the loss of that increment of total metabolism previously contributed by the fetus.¹⁷

Chart 1 shows retention of sodium throughout almost the entire period of study. It must be kept in mind, however, that urinary sodium is the only excreted sodium measured. Freyberg and Grant¹⁸ have found that from 65 to more than 200 mg. of sodium are eliminated through the skin of normal adult individuals during normal activity, in twenty-four hours. It is reasonable to assume that our patient eliminated approximately 0.1 gm. of sodium daily through the skin, in which case there was less sodium retained than represented in our data. During the periods of greatest gain in body weight (December 30 to January 1, January 5 to 7, January 23 to 25, and February 1 to 3) sodium (and water) was retained in amounts greater than usual. In order to study the effect of an abrupt increase in the intake of sodium, 5 gm. of NaCl were fed daily from February 1 through February 6. There was a retention of 3.65 gm. of sodium and of 1,001 gm. of water in excess of that used in the formation of new tissue, during the first three days of this period. During the second three days, only 0.78 gm. of sodium was retained, and the elimination of water exceeded the intake by 201 gm. On the first day after the high intake of sodium was stopped, the elimination of sodium could not be accurately measured because parturition occurred. The sodium balance was negative on February 8 and 9; on February 10 it again became slightly positive, indicating that the elimination of the added sodium had been completed. This response to feeding NaCl is identical to that observed in a normal nonpregnant individual by Wiley and Wiley.¹⁹

Newburgh's method for determining insensible loss of weight gave gratifying results in this subject. During the last forty-two days of pregnancy the amount of water vaporized is strikingly constant. Likewise, during the first six days post partum the water vaporized was very nearly the same each day.

When one considers the exchange of water along with the body weight, it is observed that just as in the case of sodium, there was retention of water during each period in which the weight increased more rapidly than usual. Likewise, each time the body weight decreased (January 8 to 10, and 17 to 19), negative water balance was recorded. One thousand and one grams of water were retained in excess of that needed for the formation of new tissue during the first three days of the period of high sodium intake (February 1 to 3); this retained water, along with the positive energy balance which obtained during this time, accounts for the sharp increase in body weight observed (a gain of 1252 gm.).

In computing water balance, four sources of water must be considered. Three sources always contribute to the total, namely, water drunk, water of food, and water formed by the oxidation of the metabolic mixture. To the sum of these three increments is *added* a fourth source, the "preformed water" liberated, if body tissue is burned, as part of the metabolic mixture; if new tissue is formed, the water used in the formation of it is *subtracted* from the sum of the first three sources. So the value for "preformed water" may be *plus* or *minus*. The algebraic sum of all four items is therefore *not* merely the water intake, but is "available water." It is this available water with which the total water lost from the body is compared in computing water balance as presented in Table I and Chart 1.

During the fifty-three days of pregnancy when water exchange was measured 151,491 gm. of water (the sum of all water drunk, water of food, water of oxidation, and water liberated by destruction of body tissue) needs to be accounted for. The total amount of water lost from the body by all avenues of excretion during this time was 148,679 gm. Thus, there was a gross retention of 2,812 gm. of water. Of this 2,812 gm. of water, 931 gm. entered into the formation of body protein and fat, leaving 1,881 gm. of water still to be accounted for. Our subject responded to a sudden increase in sodium intake in a normal manner, which is at first a retention, and later, a corresponding loss of water. However, the occurrence of parturition did not give us the opportunity to record the loss of water. Therefore, it is necessary to subtract the amount of water retained, 1,001 gm., in order to arrive at

patient with water to compensate for the loss by sweating, hyperventilation, and the inability to obtain water during labor. In the lower animals this mechanism seems to function perfectly. Personally, I think it is possible to pick up positive evidences of toxemia earlier in other ways than by the observation of an excessive gain in weight. What to do about excessive storage of water in the absence of toxemia we do not know, since we have had no idea of what the process is.

DR. HAROLD S. MORGAN, LINCOLN, NEB.—Dr. Freyberg and his co-workers have shown convincingly that the pregnant woman reacts to changes in water balance as does the normal nonpregnant woman. The translation of these thoughts into the realm of clinical obstetrics is intriguing. We have constantly before us the picture of the pregnant woman suddenly showing a marked increase in weight. This increase in body weight we have been taught to consider an early manifestation of toxemia, appearing in most cases before there is any rise in the blood pressure.

It has been our experience that it is entirely possible to handle this type of patient along the lines indicated by Newburgh and Freyberg in other communications. It is a rule in our practice to weigh every obstetric patient at every visit to the office. The patient is, of course, weighed without her clothes. If perchance a sudden excessive gain in weight is noticed during the last trimester, the patient is promptly placed on a restricted regime which may be detailed as follows: (1) All salt removed from the diet. (2) Intake and output of fluids approximated as closely as possible. (3) Increased rest, fresh air, and sedation if necessary. (4) Return to the office in forty-eight hours.

If at the end of forty-eight hours she has not lost her retained water, 10 gr. of ammonium chloride, three times a day, are administered.

Our usual experience is that patients showing this syndrome will after four or five days of careful attention, lose their water and simply by keeping on a salt-free diet and water imbalance, i.e., slightly lower intake than output, progress normally throughout their pregnancy. It is to be admitted that the odd patient will not respond and will slowly develop a rising blood pressure with a later albuminuria. It is our feeling that this patient is in a precarious condition and serious consideration should be given to the question of termination of pregnancy.

DR. FREYBERG (closing).—It would be interesting to call to your attention that Straus has reported the production of the signs and symptoms of toxemia of pregnancy resulting from water retention induced by feeding various sodium salts when hypoproteinemia exists. In the absence of hypoproteinemia the feeding of sodium salts did not produce symptoms of toxemia, and the results were similar to those in our patient when sodium chloride was fed.

Dr. Morgan noted that the treatment of his patients with toxemia of pregnancy that had edema was being carried out along the lines suggested by our experience in patients with edema accompanying chronic nephritis. In these patients we consider two points as being important. First, we make every effort to prevent the retention of sodium by feeding a low sodium diet and by having the reaction of the ash of that diet neutral, because we have observed that an alkaline ash diet will favor the retention of water. Second, we make every effort to remove the sodium that has been retained. When retained sodium is excreted, a corresponding amount of water is liberated and removed from the body and the edema decreases. The manner that has been found most satisfactory in our experience for removing sodium is the use of ammonium chloride. When these measures are carried out it is not necessary to restrict the intake of water. One can think of a situation in which the sodium acts as a sponge in the water, and when there is no sodium the water will not be retained even though 5,000, 6,000, or 7,000 c.c. of water might be taken into the body. We think it is more important to regulate the inorganic constituents, especially sodium, entering the body rather than restrict water. In patients who have severely damaged kidneys, it is not wise in our experience to restrict the intake of water.

take was lowered to its previous level. This entire response is identical with that observed when the intake of sodium chloride is increased in a nonpregnant normal adult. These observations indicate to us that the same factors that govern water balance in normal nonpregnant individuals would be of similar importance during pregnancy. The most important of these is the regulation of the intake of inorganic elements, chiefly sodium. Prevention of retention of abnormal amounts of sodium should therefore prevent significant superhydration, regardless of the intake of water.

During fifty-three days of the last two months of pregnancy, there was a gross retention of 2,812 gm. of water; however, after deducting the amount entering into the formation of body tissue, that retained as a result of suddenly increasing the intake of sodium, and, after allocating the proper amount to the fetus, only 636 gm. could be considered as "maternal superhydration." This is not beyond the normal fluctuation of body water.

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DISCUSSION

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—This experiment is unique in establishing an element not considered previously, namely, the normal status of the individual in late pregnancy.

The excessive retention of water in late pregnancy is of considerable significance and may be taken into account in two directions; first, that the extreme retention of water as indicated by edema and rapid excessive gain in weight may mean the onset of toxemia; the other is that such storage of water up to a certain point is a protective device of nature against the dehydration which may accompany labor. A great many of us in studying patients in the prenatal period, have encountered cases that tend to show the error of too great dependence upon this finding as indicative of impending toxemia, in that many women who gain rapidly in weight are, as far as we are able to determine by subsequent study, perfectly normal. We see, on the other hand, toxic patients who do not gain in weight rapidly or excessively; this "dry" eclampsia is likely to be very severe. I have always thought that water storage in late pregnancy is primarily an effort of nature to supply the

permit the condition of the patient to improve to a degree consistent with undertaking the larger operation. The cecostomy is far enough away from the midline to easily avoid contamination. Spontaneous closure of the cecostomy occurs unless special precautions are taken to keep it open.

Exploration of the abdomen includes inspection of the liver, glands along the abdominal aorta, the regional glands, the location and fixation of the growth. Involvement of the liver or aortic glands prevents any probability of cure of the carcinoma but does not preclude the desirability of a resection for the comfort of the patient. Co-existing lesions in the pelvis are examined and treated as indicated. In one instance, the omentum was incarcerated in an inguinal hernia, the aortic glands extensively involved and the growth in the sigmoid was fixed to the sacrum and pelvic wall, rendering the case inoperable. In addition, there was a large carcinoma of the right ovary which was easily removed. In another instance



Fig. 1.—Photograph to show section and ligation of the vessels far away from the bowel to preserve the anastomotic loops.

the aortic glands were extensively involved, but the rectosigmoidal growth was operable and was removed. The appendix, both tubes and ovaries and the uterus were also removed, because there was an acute and chronic inflammation of these structures.

Preservation of adequate circulation to the portion of bowel to be retained is essential. This can be readily determined by the change in color of the bowel after the vessels are sectioned. There is considerable individual variation in distribution of the vessels to the sigmoid. In case too much of the bowel is accidentally devitalized, a colostomy may be done. The pattern of the blood vessels can be demonstrated by transillumination of the mesentery but is obscure in some obese patients. When the mesentery of the sigmoid is stretched, the location of the superior hemorrhoidal and inferior mesenteric vessels is indicated by the fold of mesentery which contains them. It is desirable to section the vessels near their origin and as far from the bowel as possible in order to preserve the anastomotic loops (Fig. 1). If the vessels in the fold of the mesentery are obscured by fat,

ONE-STAGE OPERATION FOR RESECTION OF THE RECTO-SIGMOID AND RECTUM FOR CARCINOMA (WITH OR WITHOUT HYSTERECTOMY)*

I. COMBINED ANTERIOR AND POSTERIOR RESECTION

II. COMBINED ABDOMINOPERINEAL RESECTION

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THE ideal treatment of carcinoma of the rectum and rectosigmoid is complete extirpation with restoration of continuity of the bowel. No artificial anus can equal the comfort of the natural mechanism. The value of a method will be determined by low mortality, high rate of operability, possibility of wide excision and consequently a high percentage of cures. A one-stage procedure is preferable if the hazard of operation is not increased. Difference in pathology and anatomic arrangement prevents accepting a single standardized procedure. A combined anterior and posterior resection or abdominoperineal resection is applicable to nearly every carcinoma of the bowel below the level at which a Mikulicz operation is possible. When the uterus is involved, hysterectomy may be included in the resection. These operations involve procedures which are closely akin to other gynecologic problems. The method here reported is the result of experience with 40 patients operated upon since 1924.

METHOD

Preliminary biopsy of the growth through the proctoscope verifies the diagnosis. Deep x-ray therapy precedes the resection by four to six weeks. During this period the general health of the patient is treated with particular attention to under-nutrition and anemia. The patient's blood is grouped and matched with a suitable donor. For two days preceding the operation, the patient is restricted to a low residue, high caloric diet. The lower bowel is prepared by cathartics and enemas.

The abdominal part of the operation is similar for both the posterior and perineal resections. Hysterectomy may be combined with either, but delivery of a large mass is easier through the perineal incision.

The incision preferred is paramedian or median extending from the umbilicus to the symphysis. In obese patients, it may be necessary to extend the incision above the umbilicus. A right or left rectus incision is satisfactory, but in general, it gives a less adequate exposure. Since the abdominal procedure is completed without opening the bowel, the incision may be closed without drainage.

A preliminary cecostomy should be performed for decompression when an existing obstruction does not yield to simple measures. The time elapsing between cecostomy and resection varies with the individual but should be long enough to

*Presidential address read at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists at Dallas, Texas, October 14 to 16, 1937. (Illustrated by Cinema.)

The privilege of treating the women with carcinoma of the rectum and rectosigmoid is due to the courtesy of R. D. McClure, M.D., Surgeon-In-Chief, Henry Ford Hospital.

The assistance of my associates, Merrill Smeltzer, M.D., and Milo Ritter White, M.D., is acknowledged.

For the posterior resection, the patient is placed in Sims' or lithotomy position. An incision is made between the anus and the tip of the coccyx. The fascia and levator muscles are divided in the midline, opening the free space in the pelvis made by the abdominal dissection. The loose bowel is drawn through the incision and the redundant loop excised giving the growth a wide margin (Fig. 5). The



Fig. 3.—Showing the mobilization of the bowel in the abdomen and pelvis. Through the abdominal incision this dissection is continued to the tip of the coccyx.



Fig. 4.—Showing the closure of the peritoneum. The bowel has been tucked into the pelvis. The pelvis is isolated from the abdominal cavity.

cut end of the sigmoid is anastomosed to the cut end of the rectum by a few sutures. Many sutures interfere with the circulation of the bowel and result in sloughing. The anastomosis, when returned to the pelvic cavity, lies directly within the incision which provides a vent during healing and restoration of continuity of the bowel. A single drain is placed beside the bowel to promote the escape of serum

they may be exposed by incising the peritoneum and dissecting the fat. Ligation of the inferior mesenteric blood vessels early in the resection controls most of the bleeding. The middle hemorrhoids are encountered late in the mobilization of the rectum. It is simpler to ligate these during the anterior part of the resection.

Mobilization of the bowel is begun by sectioning the mesenteric vessels. It is continued by incising the peritoneum of the mesentery along each side close to the bowel except at the level of the growth where a wider margin should be taken (Fig. 2). If the uterus is to be retained, the lateral incisions of the peritoneum are connected by a transverse incision at the level of its reflection from the bowel to the cervix and vagina. If complementary hysterectomy is included, the incision of the peritoneum is continued into the incision of the broad ligaments. The ureters are not exposed or endangered if the peritoneal incision is kept close to the bowel. The next procedure is the loosening of the bowel by blunt dissection with the fingers and scissors (Fig. 3). The loose fat yields readily except at the level



Fig. 2.—Showing the incision of the peritoneum close to the bowel except at the level of the growth. This leaves an abundance of peritoneum for subsequent closure of the abdominal cavity from the denuded pelvis.

of the growth. The pathologic variations and the anatomic relations determine the procedure of loosening the growth in each individual case. The dissection from the abdomen is carried to the tip of the coccyx or below it. While freeing the bowel from the sacrum, special attention is given to the lateral sacral vessels, particularly where they enter the sacral foramina. Injury to the veins at this point may lead to uncontrollable hemorrhage.

The pelvic peritoneum is closed after all bleeding is controlled and the loose bowel tucked into the pelvic cavity. If hysterectomy has been performed, the closure is begun at the bladder. Without hysterectomy, the closure is begun at the cervix. Ample space is left at the upper end of the suture line to permit free passage for the sigmoid. In obese patients with a small pelvis, the line of incision is filled and no closure is needed. The break in the peritoneum is thus repaired and the abdominal cavity separated from the raw area of the denuded pelvis (Fig. 4). The omentum is drawn into the lower abdomen, and the incision in the abdominal wall is closed without drainage.

be extended around the anus to include as much skin as is indicated (Fig. 6). A portion of the posterior vaginal wall may be excised if that structure is involved. The resection may include the anus, sphincters, the greater part of the levators and their fascia as indicated. The dissection is continued upward from the incision in the skin and vaginal mucosa to meet the dissection already completed in the abdomen. The anus, rectum, and rectosigmoid are now free and are drawn through the perineal opening (Fig. 7). The redundant bowel is excised. A rubber tube is sutured into the cut end of the sigmoid. The perineum is repaired loosely. The bowel may be attached to the skin edge by a few sutures. Emphasis is placed on a wide excision and a loose closure. The perineal like the abdominal colostomy functions best when there is a wide opening. A drain placed beside the bowel provides an exit for any serum or blood that accumulates in the pelvic cavity (Fig. 8). If the bleeding has been controlled, the drain is not needed longer than twenty-four or forty-eight hours. In a few instances the drain came out during the transfer



Fig. 7.—Photograph (retouched) to show the liberation of the bowel completed and drawn through the perineal opening.

from the operating table to the room without any apparent harm to the patient. The catgut sutures holding the tube in place dissolve after a few days. The incision has been protected in the meantime from local soiling. Healing has advanced by this time to protect against the spread of infection.

Hysterectomy combined with the resection is essential if the uterus is involved by the growth or shows any other important pathologic change. A complementary hysterectomy is useful in some cases to facilitate the operation by providing a better exposure. It adds very little to the operative procedure and, in fact, may shorten the operating time. Any type of complete hysterectomy to which the operator is accustomed may be chosen. Delivery of the uterus attached to the bowel offers no difficulty in the abdominoperineal resection. The limited size of the incision in the combined anterior and posterior resection may complicate the delivery with the uterus attached. This factor should be considered in choosing the type of operation. Closure of the vaginal vault when hysterectomy is combined with the

and blood from the pelvic cavity. This is apparently not important and may be omitted. The drain is removed in twenty-four to forty-eight hours. The posterior incision usually closes spontaneously. Secondary closure is necessary in some instances.

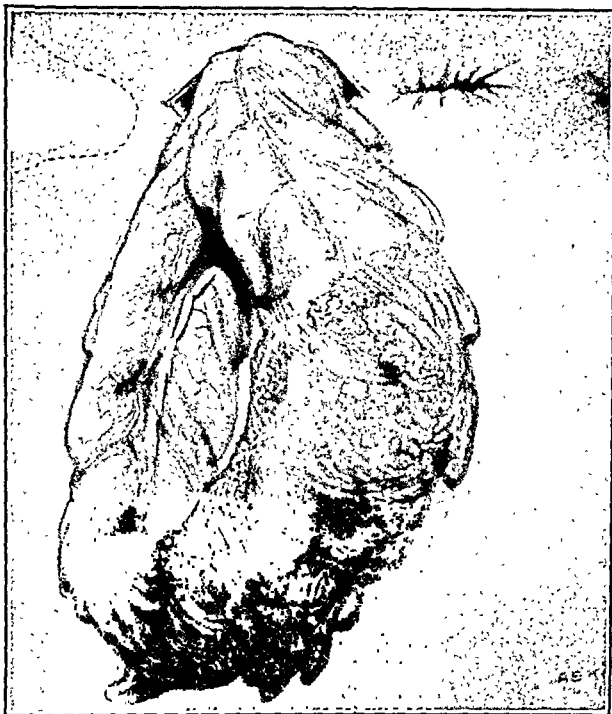


Fig. 5.—Showing the loop of mobilized bowel drawn through the incision between the anus and the tip of the coccyx.

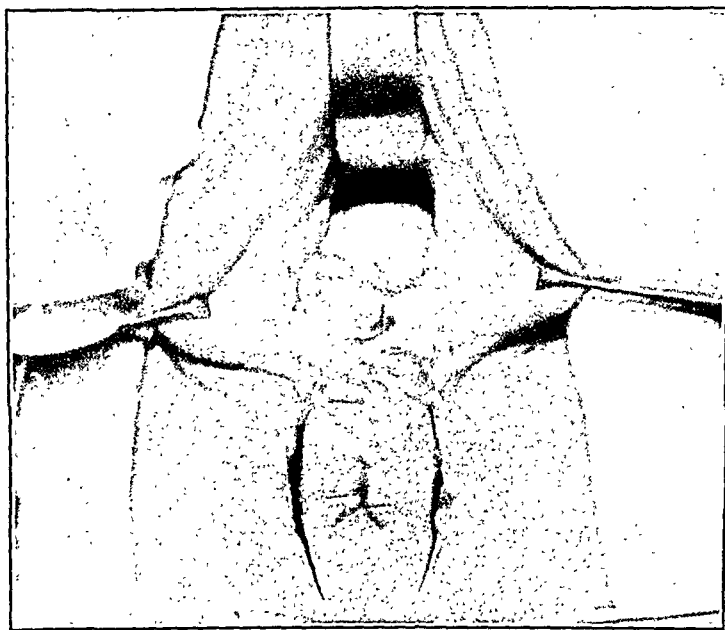


Fig. 6.—Photograph (retouched) to show an exaggerated midline episiotomy extended around the anus. An extensive growth involved the rectum to a point 2 cm. above the anus in this case.

The perineal resection is combined with the abdominal operation when the rectum and anus are involved by the growth. The perineal operation varies according to the location and character of the growth. An exaggerated midline episiotomy may

ficiently to prevent infection of the wound. In the posterior resection, drainage through the incision appears after a few days and mild local infection occurs which causes some soreness, but the infection has not spread upwards to the pelvic cavity. As healing of the anastomosis progresses, the continuity of the bowel is re-established and drainage through the incision ceases.

Healing of the posterior incision is usually spontaneous. Secondary closure has been necessary in two instances. The period of healing varies with the individual. It is a matter of weeks. While the duration of local inflammation is generally limited to a few days, one case developed an abscess in the subcutaneous tissue which drained



Fig. 9.

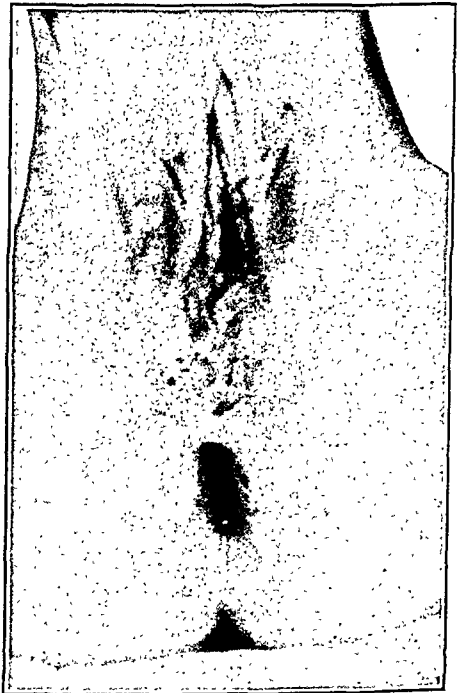


Fig. 10.

Fig. 9.—Photograph of the perineum of the first patient in whom the combined anterior and posterior resection was done. This photograph was taken thirteen years after the operation.

Fig. 10.—Photograph of the perineum two months after abdominoperineal resection. The bowel retracted but the epithelium grew in from the skin to meet it.

through the incision. Since the incision is in the midline, the tissue tends to fall together. The resulting scar is minimal. The anus retains a natural appearance (Fig. 9).

Healing of the perineal incision varies with the extent and character of the excision. Suture of the cut edge of the skin to the cut end of the sigmoid promotes quicker healing, but there is the danger of further retraction of the bowel. It may be desirable to leave some of the bowel protruding beyond the skin. After healing

abdominoperineal resection is similar to the same part of the operation in vaginal hysterectomy. The vagina is closed from above when hysterectomy is combined with the anterior and posterior resection.

The amount of tissue that can be removed by either of the operations is almost unlimited. The growth can be given a wide margin. The regional lymphatics and those accompanying the superior hemorrhoidal vessels are included in the excision. The prime requisite (radical excision) of a satisfactory operation for cancer of the rectum and rectosigmoid is easily accomplished.

The postoperative care includes an immediate transfusion in all cases. A suitable donor whose blood has been matched with the patient is available as soon as the operation is completed. Surgical shock has rarely been encountered, although it was

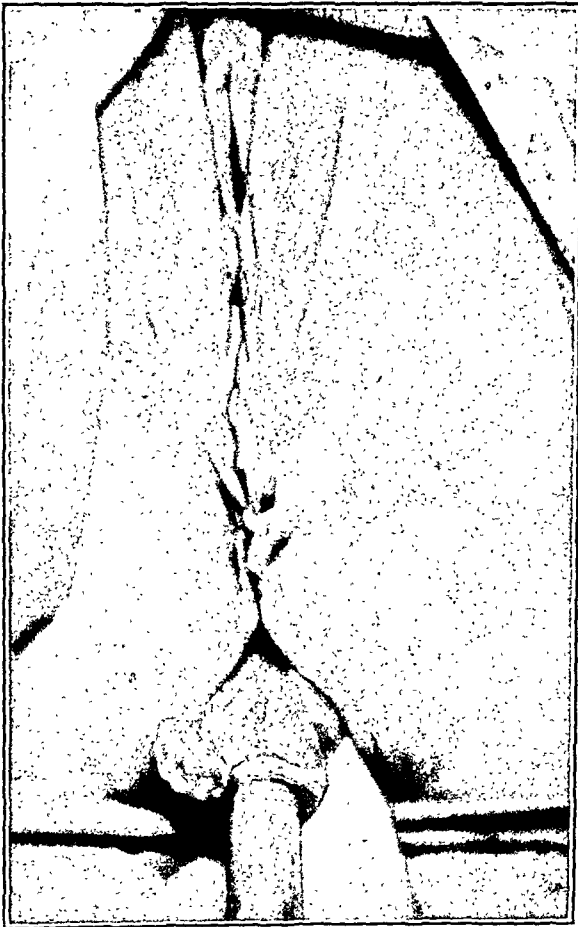


Fig. 8.—Photograph showing the perineum closed, a tube sutured into the cut end of the sigmoid and a drain placed beside the bowel to permit the escape of serum from the pelvic cavity.

responsible for one operative death. In this instance some difficulty was experienced in obtaining a suitable donor until surgical shock was manifest. It is an extensive operation at best; therefore, blood transfusion is an excellent preventive measure. Many patients might not need the transfusion, but it seems good judgment to give the blood rather than wait to see if it is needed.

The diet is similar to that given in other abdominal operations. Solid food is withheld for two days, then a low residue diet is preferred. The patients are often already debilitated and require a liberal diet to promote wound healing. Oil is given freely to keep the stools soft. Enemas can be given if indicated but are seldom required because drainage from the bowel is free.

The tube in the cut end of the sigmoid prevents local soiling of tissue until the sutures absorb and the tube drops out. By that time healing has progressed suf-

5. An obese woman, aged 51, had severe diabetes, hyperthyroidism and arterial hypertension (190/110). The carcinoma arising in the rectosigmoid had perforated the wall and extended into the uterus. An abscess had formed at the site of the perforation. An abdominoperineal resection with hysterectomy was performed. Wound infection and cellulitis of the buttock developed. She died of cerebral thrombosis on the twelfth postoperative day.

6. A feeble woman, aged 71, had an advanced carcinoma of the rectosigmoid with extensive metastases to the aortic glands. She had partial obstruction which was somewhat relieved following x-ray therapy. At operation, the growth was fixed to the pelvic wall. A cecostomy would have been better judgment. An abdominoperineal resection was done. Following operation, she apparently realized the nature of the condition and refused to eat. She was given repeated transfusions and intravenous feedings. She died on the sixtieth postoperative day.

In reviewing these postoperative deaths, four were deemed preventable. Profiting by the experience gained in these, similar instances should not occur. The last two were inoperable and should not have been done. Without operation, there is little to offer. Other cases with extensive metastases in the liver and the aortic glands have been relieved by resection and the family pleased with the added comfort and length of life. It is important to determine how far the limits of operability can be extended. This attitude, however, will not improve mortality statistics. In this series the operative mortality is 15 per cent.

Curability is difficult to summarize. Without separating the palliative operations, among all the patients operated, 7 out of 11 (63.6 per cent) lived five years or longer; 11 out of 17 (64.8 per cent) lived four years or longer, and 12 out of 20 (60.0 per cent) lived three years or longer. Operability was 95 per cent.

Wilson, Henry: Psychogenic Headache, *Lancet* 1: 367, 1938.

Seventy-five patients in whom pain in the head was a prominent symptom were studied. These included 39 women and 36 men in all of whom a physical examination had revealed no disease.

No type of pain was found characteristic of the psychogenic headache. The onset is frequently forgotten and is often the result of an evolutionary process beginning as a headache of simple worry.

Psychogenic headaches may be classified as follows:

Type 1. Headaches accompanying simple worry, readily recognized by patients as due to disquiet about current concerns.

Type 2. Headaches incidental to anxiety states, in which cardiac, gastric, or other symptoms are prominent.

Type 3. Chronic headaches, often of the pressure type, occurring especially in rigid individuals who show signs of emotional immaturity.

Type 4. Headaches conforming to description of hysterical pains, in that a single symptom is present without signs of anxiety or obsessional conditions, but in which a history reveals that the headache has been a substitute for these, or in which its disappearance is followed by the emergence of anxiety conditions.

Type 5. True hysterical headaches, not preceded by other neurotic conditions.

In the first two types the prognosis is best but depends largely upon the flexibility of the personality. Out-patient therapy consists in obtaining an adequate history, discussing environmental strains, and reviewing the patient's capacity for adjustment.

CARL P. HUBER.

is complete, the redundant bowel can be removed flush with the skin. The longitudinal muscles of the sigmoid contract causing a thickened ring of circular muscle which serves as a sphincter. Even if the bowel sloughs above the skin margin, the epithelium of the skin and bowel unite later to line the canal (Fig. 10). The perineum has a remarkable immunity to infection.

DISCUSSION

The outline of operations presented does not assume that the ideal treatment for carcinoma of the rectum and rectosigmoid has been found. It offers a choice of procedures which can be applied to almost any growth of the bowel below that level at which a Mikulicz operation can be performed. Possibility of variation in the method as the operation proceeds, extends the application to advanced growths.

Formerly, my conviction was that a colostomy was essential to a wide excision. One patient challenged that idea unintentionally.

A woman of 44 presented herself in 1924 for treatment of a carcinoma of the rectosigmoid. She refused operation if she were compelled to have a colostomy. In order to persuade her, the nature of the lesion was explained and her future predicted if she did not have the operation. Persistent refusal of the colostomy led to doing a one-stage anterior and posterior resection with preservation of the sphincters. Her recovery and thirteen years of comfort have stimulated the attempt to extend the usefulness of a one-stage resection without colostomy.

Carcinoma of the rectum and rectosigmoid is relatively less frequent in women than in men. During the last thirteen years, the one-stage resection has been done in only forty women. This series is too small to permit drawing any sweeping conclusions. Critical analysis of results is essential, however, to determine the value of the operation and to suggest modifications to be tried. Rather than present detailed case reports of all the patients, it seems more pertinent to consider briefly the six operative deaths.

1. This patient, aged 56, was in good health and general physical condition. Her lesion was early and operable. She was in good condition when she left the operating room and was not given a transfusion. Shock developed four hours later, and the patient died before a transfusion could be arranged. In retrospect, this was a preventable death if transfusion had been given earlier. Since this occurrence every patient is transfused immediately after operation.

2. This woman, aged 56, was in good general health. The lesion was local without metastases or extension. During the mobilization of the bowel from the sacrum, the lateral sacral vessels were injured. They retracted into the sacral foramina. She died on the operating table from hemorrhage and shock.

3. This woman, aged 59, was obese but her health and physical condition were consistent with her age and weight. Determination of the point for ligation of the vessels was difficult. The remaining anastomotic circulation was inadequate. The bowel sloughed followed by local infection and peritonitis. She died of terminal bronchopneumonia on the fifth postoperative day.

4. The patient, aged 66 was debilitated. She had asthma, chronic bronchitis and chronic myocarditis. The lesion was operable. The operation was not difficult. She left the operating room in good condition. She died on the fourth postoperative day from a myocardial failure. The importance of a recent cold and sinus infection had been overlooked.

mitted that there is not sufficient evidence to prove that it is pathogenic of itself." This work has as yet not been verified, and therefore we consider the results inconclusive at this time.

To us, the confusion in the minds of the gynecologists regarding the disease is evidenced by the diversity of remedial agents advocated in its treatment. These vary from douches of all colors and concentrations, powders, vaginal suppositories, and tablets, to ointments, tampons and packs.

It has repeatedly been shown by many observers that the trichomonad may be present for long periods of time in the vaginal secretion without producing symptoms, and we have at the present time under observation 19 patients, all of whom have harbored the parasite for periods ranging from five months to a year and show no clinical evidence of a vaginitis, and in whom repeated smears fail to show the streptococcus in question. Likewise, it has been definitely proved by us and others that the trichomonad can still be found in the vaginal secretion after the patient has been rendered symptom-free by our own method of treatment or by any of the numerous other methods advocated today. Also, we have repeatedly seen cases having all the clinical manifestations of so-called *Trichomonas vaginalis* vaginitis which fail repeatedly to reveal the presence of the parasite in the discharge, postmenstrual or at other times. To us, at least three possible explanations suggest themselves concerning the clinical observations so far made by the workers in this field: (1) an independent causative agent other than the trichomonad may produce this clinical syndrome; (2) the symbiotic relationship between the trichomonad and the streptococcus as suggested by others may be the causative factor; (3) the failure of patients harboring the parasite to exhibit clinical manifestations of vaginitis may be due to individual immunity established for one or both of these organisms. In this presentation we shall deal chiefly with the first of these possibilities.

The organism isolated from our cases has been positively identified as the *Streptococcus subacidus* of Holman. From our observations, which check with those of Holman and Bergey, it has the following characteristics: it appears as a slightly elongated small diplococcus, noncapsulated, and develops short chains on blood agar or in broth. In the sugar media it ferments dextrose, sacchrose, maltose, levulose and trehalose, while in 13 other sugars no fermentation is produced. The zone of hemolysis on blood-agar plates is narrow and not as definite as in other strains of hemolytic streptococci, and no green coloration was noted. They are gram-positive, and are killed in ten minutes by a temperature of 65° F., which definitely distinguishes them from the *Streptococcus fecalis*. Holman says of them: "They are not common, and the sources would suggest that the majority of the strains are highly pathogenic. They have high invasive power, and attack tissues in a state of low resistance. Clinically, the cases are characterized by a chronic, mild course, with frequent exacerbations."

FURTHER OBSERVATIONS ON THE ROLE OF STREPTOCOCCUS IN SO-CALLED TRICHOMONAS VAGINALIS VAGINITIS*

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IT IS our purpose in this paper to establish further the significance of a specific strain of streptococcus as the causative factor in so-called *Trichomonas vaginalis* vaginitis. This work is a continuance of that done by one of us (G. F. H.) in 1932. The clinical material was obtained from the Departments of Obstetrics, Gynecology and Bacteriology of the University of Illinois College of Medicine, and from private practice. All bacteriologic investigations were carefully performed and controlled under the direction of Prof. Lloyd Arnold, of the Department of Bacteriology of the University of Illinois College of Medicine.

A survey of the literature clearly shows that the role of the *Trichomonas vaginalis* in acute inflammatory conditions of the vagina has not scientifically been determined. This conflict of opinion has existed ever since the parasite was first discovered by Donn  in 1837. Scanzoni in 1856 was the first to attempt to establish its pathogenicity and to discuss the symptoms and treatment of the condition. He was followed in later years by Massa in 1885, Marchand, 1894, N. S. Davis, 1896, Mazanti, 1900, Brumpt, 1913, Hoehne, 1916, and others, all of whom attempted to further the work of Donn . DeLee in 1918 was really the first clinician to emphasize the significance of the trichomonad and undoubtedly stimulated the more recent group of workers in this field, among whom are Bland, C. H. Davis, Stein and Cope, Cornell, Goodman, Karnaky, Furniss, Rowlett, and others. These men have tried not only to verify the work of the early observers but also have concentrated upon the treatment of this condition. In spite of the careful work done in this regard, the problem is far from solved. However, the literature is by no means lacking in work done to question the pathogenicity of the trichomonad, and the recent work of Hesseltine, Plass and Borts, Adair, Allen and Jenson, Jacoby and Der Brucke, Hibbert and others, clearly demonstrates both in the laboratory and clinic that there may be other causative agents working either independently of the parasite causing the disease or in symbiosis. Craig and Faust in their recent publication of 1937 make the following statement regarding the pathogenicity of the trichomonad—"Although the *Trichomonas vaginalis* is usually found in an abnormal vagina, and while gynecologists almost universally regard a form of vaginitis as being caused by the organism, there is no evidence of scientific value demonstrating that it is a pathogenic parasite. On the other hand there is much experimental evidence proving that it is harmless and incapable of causing any pathologic lesions. Dobell in 1926 was able repeatedly to infect the vagina of monkeys with the parasite from women without any lesions of inflammatory reaction resulting, and concluded that it is not pathogenic to normal hosts. Whether it may aggravate an already existing inflammatory condition of the vaginal tract is undecided, but it must be ad-

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to demonstrate definitely that the patient has produced a specific antibody against the organism introduced. Up to the present time this has not been done in working with the trichomonad.

To prove that an immunity can be established in experimental animals, a normal mature rabbit was given nine graduated intravenous injections of an active culture of the *Streptococcus subacidus* at three-day intervals. One week following the last injection the animal was bled and the serum collected. Agglutination tests were made at various dilutions, using the rabbit's serum against the isolated strain of streptococcus and definite clumping and agglutination of the organisms was obtained at dilutions up to 1 to 640. Likewise, to prove that the patients under treatment also developed specific antibodies, and that the immunity persisted after the patient was symptom-free, the serum of 15 patients was used against the known strain of organism and agglutination was obtained in several instances up to dilutions of 1 to 800. Three cases gave incomplete agglutination, and in three cases no agglutination was noted.

In the original work done by Hibbert, in 1932, the vaginal application of the broth filtrate was the only treatment instituted. Here of course was the clinical application of Besredka's principle of establishing a local immunity by the stimulation of the reticuloendothelial system through the absorption of the filtrate by the vaginal mucosa. In the series here reported this mode of therapy was further augmented by the repeated intradermal injections of a standardized vaccine prepared from the *Streptococcus subacidus*. The strength of this vaccine was 250,000,000 per c.c. The amount given and the intervals allowed between injec-

TABLE I. CLINICAL MATERIAL

Total number of cases showing clinical picture of trichomonas vaginalis vaginitis	84
Obstetric cases	39
Gynecologic cases	45
Cases where trichomonas was found	67
Cases where no trichomonas was found	17
Cases where streptococcus predominated	79
Cases showing extensive exfoliation and fecal flora	5

TABLE II. RESULTS OF TREATMENT

Average number of treatments necessary to render patient symptom-free	5
Cases showing exacerbations during treatment	33
Gynecologic cases remaining symptom-free for 3 months	32
Gynecologic cases improved but not symptom-free	13
Obstetric cases remaining symptom-free for three months post partum	31
Obstetric cases having return of symptoms post partum	8
Cases requiring cervical cauterization	17

tions were partially based upon the experience of Corbus* in the work done with the Corbus-Ferry vaccine for gonorrhea. The initial dose was always $\frac{1}{20}$ c.c., the amount increased by $\frac{1}{20}$ c.c. with each injection until the size of the reaction wheal was about the size of a silver dollar or slightly larger. This was obtained in a majority of the cases with

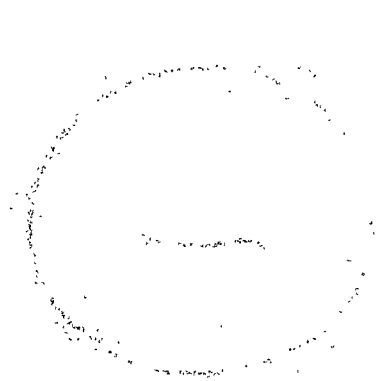
*Personal communication.

The established pathogenicity of the *Streptococcus subacidus* was proved in our work by experimental inoculation of 5 patients with a pure culture of the organism. We were successful in 4 of these cases in producing definite vaginal pathology, while in the fifth case no vaginitis was noted. The bacterial flora in all of these cases was studied and all found to be free of the trichomonad and could be classified as normal. Two of these 4 women had suprapubic hysterectomies performed during the preceding year, while the other two were menstruating normally. It was of interest to note that in the latter two cases the vaginitis was more acute, the symptoms more pronounced, and the growth of the implanted streptococcus was much more profuse. Objectively the symptoms produced were intense redness of the cervix, vaginal mucosa and vulva, and a gray-white, sticky discharge. Subjectively the patients all complained of a tenderness, burning and itching about the vaginal orifice, and a whitish discharge that "scalded the parts," as one patient explained.

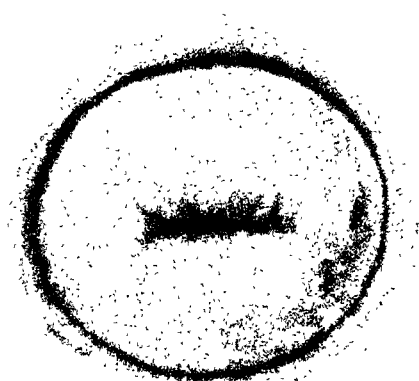
The inoculation was done by applying an active broth culture to the vagina with a sterile cotton swab, and a wick-like sterile cotton tampon soaked in the culture was allowed to remain in the vagina for twenty-four hours. During the period of observation before treatment was instituted the patients were instructed to refrain from coitus, to use no vaginal douches, and to be extremely careful regarding their personal hygiene and cleansing of the toilet after stool, inasmuch as the condition present was produced by a pathogenic streptococcus. The symptoms were allowed to remain untreated for three weeks in the hysterectomized patients and through one complete menstrual cycle in the other two. The treatment instituted was as follows: At no time was any bacteriocidal agent applied to the vagina; the vaginal tract was first cleansed of accumulated debris with dry, sterile cotton. Then a sterile cotton tampon saturated with a broth filtrate of the *Streptococcus subacidus* was packed against the cervix and allowed to remain in place for twenty-four hours before removal by the patient. An intradermal injection of a standardized vaccine made from the *Streptococcus subacidus* was also given at this time. The interval between treatments was one week, and the treatments were discontinued during menstruation. All four of these patients were successfully treated and rendered symptom-free in from four to seven treatments. They report to us once a month for smears and observation, and they have absolutely been symptom-free for periods varying from three to six months.

To us, this series, while limited to only four cases, is of great importance, not only in definitely establishing the pathogenicity of the *Streptococcus subacidus*, but also from the clinical experimental standpoint we were able to fulfill Koch's postulates inasmuch as the following was accomplished: (1) the successful inoculation of a normal patient with a pure strain of a known organism, (2) the reproduction of the characteristic pathology in the host, (3) the recovery and re-identification of the organism from the lesion produced, (4) the successful treatment of the patient by the use of a vaccine made from that organism, and in our cases also by the local use of the broth filtrate, and (5)

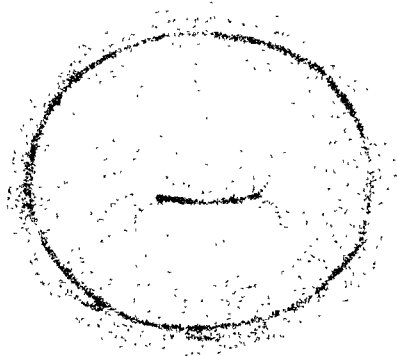
ACUTE VAGINITIS PRODUCED BY INOCULATION WITH STREPTOCOCCUS SUBACIDUS



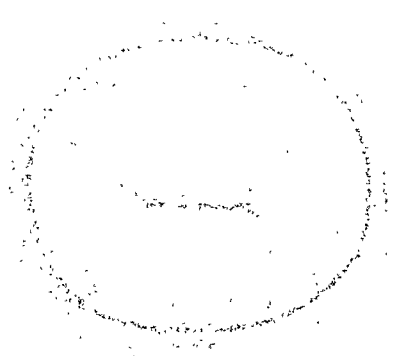
DISCHARGE OF VAGINAL CANAL
 BEFORE INOCULATION



SAME SUBJECT TWO WEEKS
 AFTER INOCULATION



AFTER THREE TREATMENT



AFTER FIVE TREATMENT

trichomonads were present in large numbers, but definitely associated with the *Streptococcus subacidus*. Our experience in cases having repeated postmenstrual exacerbations showed that the pH might change rapidly; the reading before the

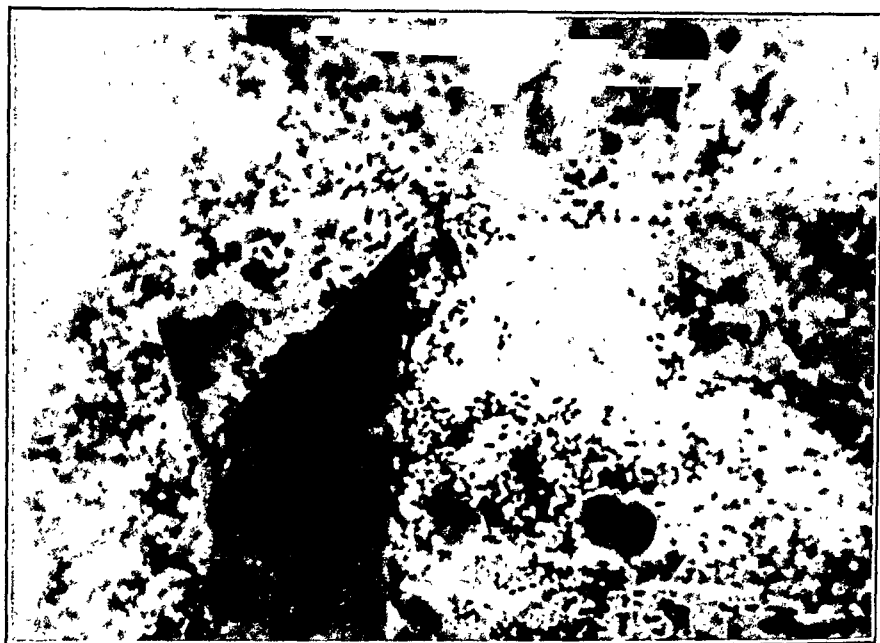


Fig. 1.—(No. 190-446.) Mrs. H., para ii, white woman in sixth month of gestation. Pregnancy was complicated by extreme tenderness of the vagina and vulva, profuse discharge, and itching. Microscopic examination of discharge: Few trichomonads were found. Gram stain: many gram-positive diplococci, pus, epithelium and associated flora heavy. Patient treated as described and followed through third month post partum. Symptom-free since ninth month of gestation. Gram stain of vaginal smear at sixth month of gestation, before treatment, showing heavy growth of gram-positive diplococci (*Streptococcus subacidus*), pus cells, epithelium and associated flora.



Fig. 2.—Gram stain of vaginal smear after five treatments in seventh month of gestation. (Note large number of autolized bacteria on plate.)

menstrual period, when the patient was symptom-free, would often be 5.0, and at the height of the flare-up it would be 6.4. A study of the hanging drop in these cases failed to show any appreciable increase in the number of trichomonads, but the Gram stain of the discharge often showed a marked increase in the number of

approximately $\frac{1}{10}$ c.c. dose. It was interesting to note in many instances that as the vaginal symptoms subsided the skin reactions rapidly decreased in intensity and duration, the patient often declaring that the dosage must be smaller because of the mildness of the reaction as compared to that following the first few injections given, when actually the amount given was often $\frac{1}{10}$ c.c. In private practice the injections were given at four-day intervals, and the dosage given usually $\frac{1}{20}$ c.c., seldom increased to $\frac{1}{10}$ c.c. because the patients were more accessible and because it was thought that better results could be obtained by this type of stimulation. However, the results did not differ from those where the treatments were given once a week in the clinic.

A brief outline with special reference to the use of the broth filtrate applied vaginally, and the intradermal injection of the vaccine is as follows:

- a. The vagina is wiped free of discharge with dry sterile cotton pledgets.
- b. At no time is any solution of germicidal nature used—no green soap nor mucus-liquefying agents.
- c. A sterile cotton tampon, approximately the length of the vagina, is saturated with the broth filtrate and inserted vaginally. This is removed by the patient in twenty-four hours. Lamb's wool tampons are unsuitable because they do not absorb and hold the filtrate.
- d. The filtrate is applied to the external genitalia where external irritation is noted, and allowed to dry.
- e. Intradermal injections of the vaccine are given on the flexor surface of the forearm every four to seven days, the initial dosage being $\frac{1}{20}$ c.c., increasing in amount gradually until the size of the reaction wheal is about two inches in diameter.

A study of the pH concentration of the vaginal discharge in connection with the cases studied was made; bromphenol blue and phenol red were the indicators used. On the whole our observations checked closely with those of Oberst and Plass, Karnaky, Cruickshank and others. In those cases having an associated cervicitis with profuse discharge before treatment, the average pH was 7.0, regardless, in many cases, of the number of trichomonads present. In these cases the bacterial flora was unusually heavy and the streptococcus could usually be found in large numbers, along with staphylococci, gram-positive rods, gram-negative bacilli, pus and debris. After treatment, and especially thermal cauterization of the cervix, the pH sometimes dropped to 4.8. When it did drop, the bacterial flora, particularly the streptococcus, would decrease markedly in numbers, as well as the trichomonad. Agglutination tests made at this time usually showed a definite active immunity established, but this was variable in some cases.

In the cases experimentally inoculated with the *Streptococcus subacidus* the average pH before inoculation was 4.8, and one week after development of the vaginitis the average pH was 6.4, but dropped back again to 4.8, 4.8, 5.0, and 5.0, respectively, as the patients became symptom-free. It was noted that in those cases where the streptococcus was the predominating organism the pH ranged from 6.0 to 7.0, perhaps indicating a more pathologic condition present, if one used the pH of 4.5 as a normal indicator, in contrast to an average pH of 5.5 to 6.5 where the

led us to believe that the number of trichomonads present in the majority of cases studied does not change in proportion to the change of pH reading as does the growth of the *Streptococcus subacidus*. It might be of interest to know that the pH of the broth before it was inoculated with the *Streptococcus subacidus* was 7.8, and the pH of the broth filtrate as we used it averaged 6.2. Whether the filtrate itself aids in the process of changing the pH of the vagina is undecided.

To clear up adjacent active foci of infection is of great importance, as is brought out by the number of cases having thermal cauterization of the cervix. Freeing the vagina of this copious discharge removes an excellent bacterial medium and aids in the efficiency of the treatment. We also had three instances of chronic Bartholinian abscesses that undoubtedly played a part in causing repeated exacerbations, and one case of an infection of Skene's glands that was destroyed by cautery. In other words, to build up the resistance of the pelvic tissues is of im-

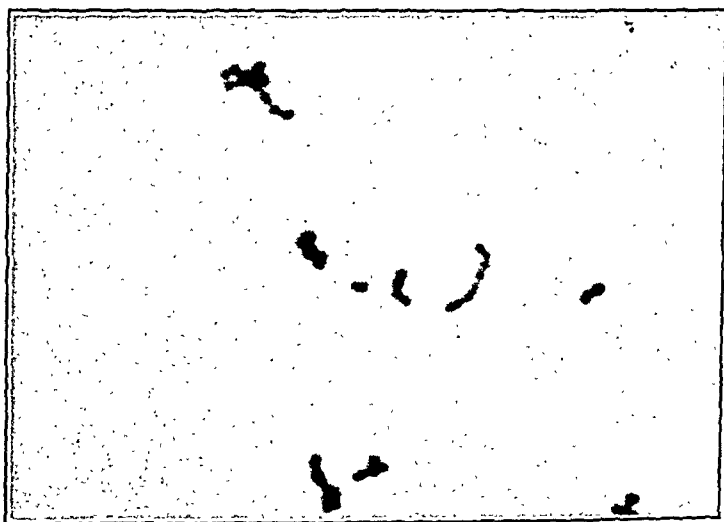


Fig. 5.—Showing *Streptococcus subacidus* from broth medium, showing chain formation.

portance, and removing any factor that prevents an establishing of normal cellular reaction and function plays a part in the treatment of these cases.

Many interesting and puzzling observations were noted in connection with our work. We were by no means successful in rendering all patients symptom-free. Some absolutely failed to respond to our therapy, for no apparent reason. However, it is of great importance to realize that the majority of patients with this type of infection can be rendered symptom-free for months without applying mechanical, thermal, or chemical means to the actual destruction of the parasite.

The possibility of transmission of this disease by coitus to the male was directed to my attention by the following case.

The husband and wife came to one of us (G. F. H.) quite upset because a diagnosis of gonorrhea had been made in both, yet both parties denied exposure. A hanging drop of the vaginal discharge showed a few scattered trichomonads, and a Gram stain of the smear showed a heavy growth of bacteria, including a large number of *Streptococcus subacidus*, staphylococci, many bacilli, and pus. The anterior

streptococci as well as the gram-positive and gram-negative bacilli, staphylococci, and pus cells. The average pH in the prenatal cases untreated was 6.8, while that in the gynecologic group was slightly lower, 6.2. In many cases showing very little discharge but a marked redness and extreme tenderness of the vagina, and showing comparatively few trichomonads but a heavy growth of *Streptococcus subacidus*, the initial pH before treatment was from 6.4 to 7.0. After several treatments, which rendered the patient symptom-free for several weeks, the pH was frequently found



Fig. 3.—Gram stain made in ninth month gestation, showing scant bacterial flora. Patient symptom-free.

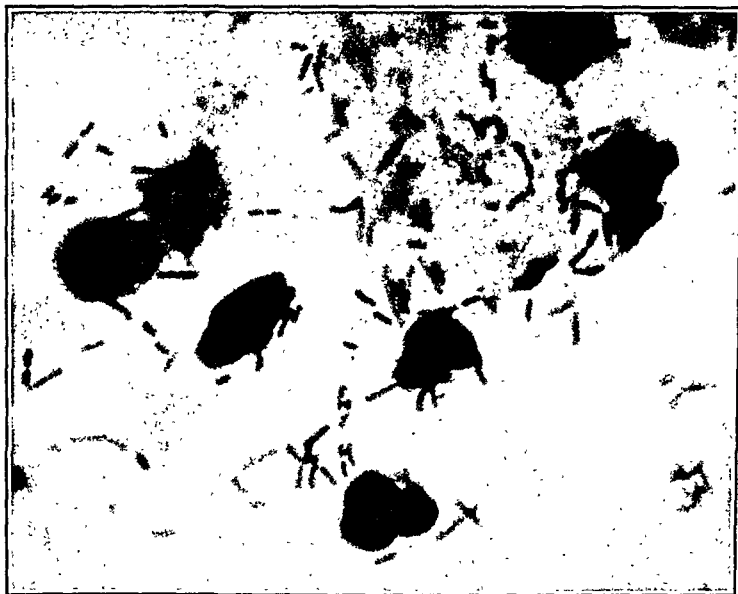


Fig. 4.—Gram stain made at tenth week post partum, showing almost pure growth of Döderlein's bacillus. Patient symptom-free for thirteen weeks.

to be 4.8 to 5.0, at the same time smears from the vagina showing very few streptococci, staphylococci, gram-positive and gram-negative bacilli, many epithelial cells, a few scattered pus cells, and Döderlein's bacilli present, although little change in the number of trichomonads was seen. This would indicate that clearing the vagina of the streptococci may have helped bring the pH nearer to normal and aided the vaginal mucosa in returning to a normal physiologic condition by raising local immunity, regardless of the parasites present. In other words, our observations

DISCUSSION

DR. FRED L. ADAIR, CHICAGO.—With this contribution Dr. Hibbert and Dr. Falls have proved the pathogenicity of *Streptococcus subacidus* in the causation of various cases of vaginitis. They have proved this especially in its association with trichomonads, but so far as I can see the role of the trichomonad is still undetermined.

When organisms in symbiosis produce a pathologic process we have to remember that any therapy which affects either organism would be likely to result in a cure. Assuming for a hypothesis that trichomonads and other organisms work in symbiosis, we might sometimes see *Streptococcus subacidus* and, in other cases, there might be other organisms. Any therapy which has a destructive effect or diminishes the activity of one of these organisms working in symbiosis would result in a certain percentage of cures.

DR. H. C. HESSELTINE, CHICAGO.—Perhaps some proponent of the idea that the trichomonads are pathogenic will point out that 29 per cent of the gynecologic group were not relieved of symptoms by the therapy employed. Such a criticism is not valid in view of the fact that no single therapeutic measure (in a sufficiently large and adequately controlled series) has removed all symptoms. The contributions by Allen, Jensen and Wood demonstrate definitely the importance of the male urinary tract as a focus for the genital reinfection. Therefore, with this and other sources of reinfection, a minority of failures may be expected. These unsatisfactory cases may well be the result of reinfection rather than a failure of the remedial agent.

In contrast to this specific therapy of Hibbert and Falls, the nonspecific lactose therapy employed at The University of Chicago Clinic in The Chicago Lying-in Hospital enhances the development of a normal bacterial flora. The normal physiologic and biologic state is unfavorable to many pathogenic agents which may attack the vagina. It seems pertinent to ask if Drs. Hibbert and Falls have studied any of the other bacteria associated with the vaginal trichomonads, particularly anaerobic ones, and some of the gram-negative small cocci which are present not infrequently in considerable numbers.

DR. KARL J. KARNAKY, HOUSTON, TEXAS.—I have been doing extensive research on *Trichomonas vaginalis* and leukorrhea for more than six years at the Jefferson Davis Hospital, Houston. I have cultured all bacteria associated with *Trichomonas vaginalis* in all culture media obtainable and inoculated them into 35 women, free of *Trichomonas vaginalis*. In these cases I obtained no itching, and in a few cases only a slight discharge. In no case did I get the typical signs and symptoms of *Trichomonas vaginalis*. But when I inoculated *Trichomonas vaginalis* and the associated organisms together I obtained typical signs and symptoms of itching and burning of the external genitalia.

I have also observed in positive cases of *Trichomonas vaginalis* with pruritus vulvae that as soon as I got rid of the trichomonads the patient became free of her pruritus. Furthermore if one will take smears every day or week, it will be noted that in a case of *Trichomonas vaginalis* which has been cured, as soon as she begins to itch again the trichomonads can be found once more. The clinical symptoms so closely parallel the vaginal smear that I am still more inclined to believe that *Trichomonas vaginalis* is a pathogenic organism.

I have inoculated pure cultures of streptococci from the throat into five normal vaginas and in one case I obtained red superficial blotches, ranging in size from a dime to the size of a half dollar. These were not like the small round discrete spots seen in some cases of *Trichomonas vaginalis*. On the other hand in a series of 4,000 positive cases of *Trichomonas vaginalis*, we failed to find the streptococci any oftener than in the non-trichomonad cases. We are inclined to believe from our clinical observations and trichomonad research that trichomonas is more likely to be the causative organism than the streptococci. Yet I am going to give Dr. Hibbert's vaccine a good trial.

urethral smear from the husband showed just a few trichomonads and a corresponding flora with the Gram stain. Prostatic secretions were, as far as could be determined, normal. This man was treated as follows: an anterior urethral injection of the broth filtrate was given twice a day, a bland diet prescribed, and plenty of fluids. In seventy-two hours all the swelling and inflammation and dysurea disappeared, and scarcely enough discharge was present to make a smear. He was symptom-free in four days and has had no recurrences. Sexual continence was advised, to avoid re-infection.

We believe that there are many phases of this work that require more elucidation, and we shall continue to study the problem further in our clinic.

From our observation may we draw the following conclusions:

1. The *Streptococcus subacidus* found in patients presenting the clinical picture of *Trichomonas vaginalis* vaginitis is pathogenic, as shown by its fulfillment of Koch's laws.

2. It produces an immune reaction (agglutination) when injected intradermally.

3. Local clinical improvement was more rapid and apparently more lasting when general antibody reaction was stimulated by the vaccine in addition to the local antibody stimulation by the filtrate.

4. The pH of the vagina was found to be relatively high when there were large numbers of *Streptococci subacidus* present, and to be lower as they disappeared, irrespective of the presence or absence of the trichomonads.

5. The disappearance of the clinical picture and symptoms with the disappearance of the *Streptococcus subacidus*, occurring in the presence of the trichomonads, suggests the former as the chief factor in the production of the lesions.

6. Further efforts to eradicate this streptococcus from the genital tract, and to raise the general immunity to this organism, seem the logical way to attempt the control of this infestation.

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A CONSIDERATION OF ARTIFICIAL FEVER THERAPY AND SULFANILAMIDE THERAPY IN THE TREATMENT OF GONORRHEAL INFECTIONS OF WOMEN*

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THE treatment of gonorrheal infection of women has undergone a marked change in the past few years. The use of the Elliott vaginal heat regulator and the vaginal application of diathermy have aided considerably in the treatment of gonorrheal infections of the female genital tract by permitting a more efficient application of heat to the pelvic viscera. Recently, artificial fever therapy has been used to treat such infections by elevating the general temperature of the patient; if the elevation of temperature is maintained for a sufficient length of time it will destroy the *Neisseria gonorrhoeae*. Local heating of the pelvic tissues by one of the two methods previously mentioned has been used in conjunction with artificial fever therapy and has resulted in an improvement in the results together with lessening the number of fever treatments necessary to effect a cure. The technic and the results of treatment with artificial fever therapy have been published in numerous articles. In more than 90 per cent of cases in which female patients have been treated by this method, consistently negative cultures have been obtained on chocolate blood agar. The failures usually may be explained by a strain of *Neisseria gonorrhoeae* that is heat resistant or by the inability of the patient to tolerate the high temperature necessary for a sufficient length of time. More recently, a further advance has been made in the treatment of gonorrhea by the oral administration of sulfanilamide. Experience in the use of sulfanilamide in the treatment of this infection of the female genital tract is as yet insufficient to permit a final evaluation of the percentage of cures that may be expected. However, conservative consideration of the data so far accumulated indicates that from 80 to 90 per cent of clinical remissions may be expected in cases in which patients are treated by this method.

We wish to report two groups of cases of gonorrheal infection of the genital tract among women. Group 1 consists of cases in which the patients were treated by fever therapy in an attempt to arrest the disease by a single ten-hour fever treatment. Thirty-seven cases are included in this group (two of the patients received the treatment combined with the administration of sulfanilamide). In addition to the usual management of the patient who is receiving a long fever treatment we feel that two factors have contributed much to the successful treatment. The first of

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In almost all vaginal infections we have a hypo-acidity. So as the result of the research of Cruickshank and Sharman and of myself, I began about four years ago to use glucose, maltose, lactose and saccharose, because they are the sugars broken down by Döderlein's bacilli, in the treatment of vaginal leucorrhœas. In America I was the first to use sugars in the treatment of *Trichomonas vaginalis*, and this I presented in an exhibit before the American Medical Association in Atlantic City two years ago, in Texas, and elsewhere. Since my first work on the use of sugars in the treatment of *Trichomonas vaginalis*, others have made similar reports.

The more mixed is the bacterial flora, the more the pH approaches the alkaline side, the fewer Döderlein bacilli are present, the less sugar is found in the epithelial cells, and the lower is the height of the mucous membrane.

We are using glucose-lactose tablet, pH 3.0-3.3, containing 1½ gr. of 5-7 diiodide-8-hydroxyquinoline. We have increased our cures, by from 10 to 15 per cent, by the addition of acids to our sugars used.

One must clear up any associated cervical infection because the highly alkaline cervical discharge (pH 8.0-9.0) neutralizes the acid of the vagina and so lowers the resistance of the vagina. We treat the patient with glucose-lactose tablets (pH 3.0-3.3) for twelve days followed by the use of vinegar douches (3 tablespoonsful to 2 quarts of tap water) and then cauterize, coagulate or cone the cervix.

I have found many cases of *Trichomonas vaginalis* with the organisms in the prostate, under the prepuce, and in the urethra of men. I have seen a convict who has been in jail for a year with trichomonads in his prostate. I now believe we cure almost all cases of *Trichomonas vaginalis*, and the small percentage that we are unable to cure are re-infections from the sexual partner.

DR. HIBBERT (closing).—It has been a question, as to what type of treatment will restore the tissues to their normal condition. I have proved definitely in my work that that can be done by nothing more than an application of a streptococcic filtrate. To apply different medicaments to the vaginal mucosa and to dry up the vaginal tract is not helping nature to restore normal conditions in that vaginal tract. In these cases I used no medicaments but I was able to get the patients symptom-free and to restore the bacterial flora, as well as the pH concentration, to normal.

Tenney, Benj. Jr., and Parker, Fred. Jr.: Significance of the Weakly Positive Aschheim-Zondek Test, New England J. Med. 218: 561, 1938.

Sixty cases that showed a weakly positive Aschheim-Zondek reaction were followed up to a definite diagnosis. The majority of these patients miscarried. In a relatively large number a tubal pregnancy was found at operation. No patient had a normal pregnancy, four patients were not pregnant.

The authors conclude that a weak positive reaction after the first few weeks of pregnancy indicates some abnormality; in the presence of signs of a threatening abortion it indicates a poor prognosis. Tubal pregnancy must always be carefully considered in this type of test. Thus a weakly positive Aschheim test may be of as much value as a positive or negative one.

HUGO EHRENFEST.

Ernst, S.: Estrogenic Substance in Cases of Milk Fistula and Mastitis, Zentralbl. f. Gynak. 61: 1420, 1937.

In 1936, Lindemann reported the rapid healing of a milk fistula which followed an incision in the breast for mastitis by administering estrogenic hormone. Ernst reports two successful results with the same therapy. In these cases, rapid cessation of secretion of milk and spectacular healing of the fistulas could not be attributed to anything but the estrogenic substance.

J. P. GREENHILL.

will quickly eliminate the drug from the body. In our experience the drug has been well tolerated by the majority of patients. Nausea may occur and vomiting occasionally is experienced. Headache, generalized aching, dizziness, and, at times, paresthesias are noted. Some patients have a sense of euphoria. In one case the patient experienced a rather pronounced febrile reaction. In this case the drug was allowed to dis-

TABLE I. A CASE IN WHICH ARTIFICIAL FEVER THERAPY FAILED TO CURE A GONORRHEAL INFECTION BUT IN WHICH SUBSEQUENT ADMINISTRATION OF SULFANILAMIDE RESULTED IN CURE

DATE, 1937	CHOCOLATE BLOOD AGAR CULTURES	FEVER THERAPY		VAGINAL DIATHERMY		SULFANIL- AMIDE GRAINS	LOCAL TREATMENT
		HOURS	DEGREES F.	HOURS	MINUTES		
3/22	Positive						
3/24		10	106+				
3/29	Positive						
3/31		10	106+				
4/ 3	Positive						
4/ 6		10	106+	2	40		
4/ 8	Negative						
4/ 9	Negative						
4/14	Positive						Begun
4/16	Positive						
4/27	Positive						
5/11	Positive						
5/13		11	106	6	15		
5/19	Positive						
5/31							Discontinued
6/ 1						40	
6/ 2						60	
6/ 3						60	
6/ 4						40	
6/ 5						40	
6/ 9	Negative						
6/12	Negative						
6/14	Negative						
6/24	Negative						

appear from the blood. Subsequently, a dose of 50 gr. (3.2 gm.) was given subcutaneously and this was followed by a rise in temperature to 103° F. The patient to whom sulfanilamide is given may assume a slate color and at times may have a true cyanosis. Some of the patients who have had these color reactions have had demonstrable amounts of methemoglobin in the blood and sulphhemoglobinemia rarely may be found. In a small percentage of cases a reduction in the number of erythrocytes and leukocytes may be noted. It is possible that any of these symptoms might become severe enough to warrant cessation of treatment. In our experience it has been advisable to discontinue the administration of the drug for a time in a few cases but the patients subsequently were able to resume the medication and complete an adequate course of treatment. One no doubt will encounter patients who will not be able to take sulfanilamide but the number of such patients will likely be small. This drug should be administered only under the direction of the physician who prescribes it and who will assume the responsibility for observation of

these is the exposure of the skin to the ultraviolet lamp for a sufficient length of time to produce a mild erythema followed by immersion in the Hubbard tank for thirty minutes and wrapping in blankets for one and one-half hours. The vasodilatation thus secured aids the patient in tolerating the prolonged fever treatment. The second factor is the intravenous injection of a 5 per cent solution of dextrose in physiologic saline solution immediately following the treatment. In those cases in which the value for the systolic blood pressure drops below 80 mm. of mercury, the intravenous injection should be commenced at once before completion of the fever treatment. This prevents the danger of circulatory collapse. All of these 37 patients in Group 1 received treatment with ultraviolet lamp and immersion in the Hubbard tank preliminary to the sessions in the fever cabinet. Thirty-one of the 37 patients received a single ten-hour treatment in the artificial fever cabinet at a temperature of more than 106° F. Twenty-two of the 31 patients who received a single ten-hour treatment received additional local heating with either the Elliott vaginal heat regulator or vaginal diathermy. In 9 cases local application of heat was not employed. Five patients were unable to tolerate the ten-hour treatment at the first attempt but were able to do so at the second treatment. Thus, 31 patients of the 37 patients received a single ten-hour session in the fever cabinet. In 29 (93.5 per cent) of these cases cultures made from the urethra and cervix on chocolate blood agar, were consistently negative. Six of the 37 patients were given multiple artificial fever treatments. Two of these received two treatments at the time we were instituting the single long fever treatments; one patient who had a severe gonorrheal arthritis received two long treatments in addition to sulfanilamide, chiefly because of the arthritis; one patient was treated three times before the cultures became consistently negative; one patient who was fifty-eight years of age and who had not responded to adequate doses of sulfanilamide was given two short treatments of five and six hours after which we obtained consistently negative cultures. One patient received four treatments in the fever cabinet; in two of the treatments additional heat also was applied locally. In spite of this treatment the cultures remained consistently positive. She was later treated with sulfanilamide when this drug became available; the cultures then remained consistently negative for the *Neisseria gonorrhoeae*. Table I is an outline of the treatment in this case. Thus, 34 (94.1 per cent) of the 37 patients treated with fever therapy were found to have consistently negative cultures following treatment. In two cases it was necessary to administer sulfanilamide in combination with the fever therapy before consistently negative cultures were obtained. In the case illustrated in Table I the results of fever therapy were considered unsatisfactory. In this instance sulfanilamide was not administered in combination with the fever therapy but was given later.

Group 2 consists of cases in which the patients were treated with sulfanilamide. The oral administration of sulfanilamide has been found to give satisfactory results as it is readily absorbed from the gastrointestinal tract. The drug is excreted almost entirely through the kidneys. In the event of an untoward effect the administration of large amounts of fluid

TABLE II. A CASE IN WHICH THE ORAL ADMINISTRATION OF SULFANILAMIDE FAILED TO CURE A GONORRHEAL INFECTION BUT IN WHICH SUBSEQUENT FEVER THERAPY RESULTED IN CURE

DATE, 1937	SULFANILAMIDE, GR.	CONCENTRATION OF SULFANILAMIDE, MG. PER 100 C.C. BLOOD	CONCENTRATION OF SULFANILAMIDE, MG. PER 100 C.C. URINE	METHEMOGLOBIN: + = PRESENT	HEMOGLOBIN, GM. PER 100 C.C.	ERYTHROCYTES, PER C. MM. OF BLOOD*	LEUCOCYTES, PER C. MM.	SEDIMENTATION RATE, MM. IN ONE HOUR	CHOCOLATE BLOOD AGAR CULTURES	FEVER THERAPY	
										HOURS	DEGREES F.
7/ 6	60	8.8		+	13.5	3.89	6,900	76	Positive		
7/ 7	20		36.5†								
			27.8†								
7/ 8	50		100.0†								
			66.6†								
7/ 9	60										
7/10	60					4.38	7,400				
7/11	60		77.0†								
			23.0†								
7/12	20		222.0†			4.27	7,000				
			177.0†								
7/13	0	Negative		+				44	Positive		
7/14	0										
7/15	0										
7/16	20										
7/17	0										
7/18	0	1.8									
7/19	20		24.0†								
			26.0†								
7/20	40	8.0							Positive		
7/21	40										
7/22	50										
7/23	50										
7/24	50								Positive		
7/25	60	9.6									
7/26	60										
7/27	70										
7/28	70										
7/29	70								Positive		
7/30	30			+							
7/31	10										
8/ 1	0										
8/ 2	0	3.1			13.65	4.22	14,000			5	106+
8/ 3	40				9.35	3.11	4,600			6	106+
8/ 4	40				11.4	3.39	6,500		Positive		
8/ 5	0	4.4		Trace				18			
8/ 6	40										
8/ 7	40					2.88	4,700		Negative		
8/ 8	40					2.72	5,500				
8/ 9	40										
8/10	40							13			
8/11	40										
8/12	40										
8/13	40								Negative		
8/14	40										
8/15	40										
8/16	30										
8/17	0										
8/18				Negative	9.75	3.53	5,300		Negative		
8/19									Negative		

*Expressed in millions. †Free. ‡Conjugated.

the patient during the duration of the treatment. A marked anemia or a renal insufficiency may be a contraindication to the use of sulfanilamide. During the course of treatment it is advisable to repeat the examination of the blood from time to time in order to be sure that a significant anemia does not develop. A slight drop in the value for the hemoglobin and in the number of erythrocytes and leukocytes is not infrequently seen but is not a contraindication to continuing the treatment.

The dose of sulfanilamide varies in the experience of different physicians and also depends on the condition for which it is used. The dose of sulfanilamide employed by us and outlined in this paper has seemed adequate for the treatment of gonorrheal infections. Treatment is commenced by the administration of 60 gr. (4 gm.) of sulfanilamide on the first day; this is divided into four doses of 15 gr. (1 gm.) each. On the second and third days 80 gr. (5.3 gm.) are administered in four doses of 20 gr. (1.3 gm.) each. Beginning on the fourth day a daily dose of 40 to 60 gr. (2.6 to 4 gm.) is resumed. At the end of a week of treatment cultures are taken from the uterine cervix and urethra. If the cultures are negative, administration of the drug is continued and the cultures are repeated in two or three days. If they again are negative, administration of the drug is discontinued. Repeated cultures are then taken until four negative cultures have been obtained. One of these must be obtained immediately following the cessation of menstruation. If at the end of a week of treatment the cultures still are positive, the treatment should be continued. Should infection still be evident in the cultures at this time it is well to ascertain the concentration of the drug in the blood. If this concentration is found to be below 6 to 9 mg. per 100 c.c., the dose of sulfanilamide is probably insufficient and will need to be increased. It is difficult at this time to state definitely how long treatment with sulfanilamide should be continued in the face of consistently positive cultures. The case illustrated in Table II reveals that a sufficient concentration may be maintained for seventeen days and still be ineffective. One must consider the fact that a higher concentration may be necessary for certain strains of *Neisseria gonorrhoeae* and therefore larger doses may be necessary in some cases.

Sixteen patients were treated by oral administration of sulfanilamide. One patient had failed to respond to adequate fever therapy. Fifteen (93.7 per cent) of these had consistently negative chocolate blood agar cultures after treatment. In one case it was necessary to administer two short sessions of fever before negative cultures were obtained. In this case the concentration of the drug in the blood was higher and the duration of treatment was longer than in the cases in which the cultures became negative. The average duration of treatment as shown in Table III was 10.5 days; the longest course of treatment was twenty-three days and the shortest five days.

The average amount of drug administered was 590 gr. (39.3 gm.), the greatest amount was 1350 gr. (90 gm.) and the least amount was 250 gr. (16.6 gm.). An average daily dose of more than 54 gr. (3.5 gm.) was used.

The actual mechanism of fever therapy has not been definitely established. The fever destroys the gonococcus, which is thermo-labile, but the human body tolerates with safety this artificial fever. At the present time, at the Washington University School of Medicine, experiments are being made to determine whether we are dealing with an immune body reaction, rather than merely with a gonococcal effect. It would seem that all immune substances which can be measured are actually increased during each session of fever therapy. Eventually, practically all patients get well, and the gonococcus is no longer found in smears or cultures at the end of the course of treatment.

At the Barnes Hospital, from Oct. 7, 1935, until Oct. 5, 1937, 211 patients have received approximately 1100 treatments. Out of this number, 21 were women who had an active gonococcal pelvic infection and an acute or chronic inflammatory gonorrheal complication. The Kettering Hypertherm has been used almost entirely for the development of the fever. Of these 21 women, none showed untoward results of any kind, and all have become free of organisms on repeated examinations. In acute cases, the tubal masses showed either definite improvement or complete resolution. In the chronic cases, the adnexal tenderness and induration has markedly diminished or disappeared entirely.

These patients received an average of 4.6 fever treatments of four to five hours each, at temperatures maintained at 106 to 107° F. The interval between treatments was two days. In all but two patients, organisms were not found after the third or fourth treatment, after which an additional treatment was given. Two patients received six and seven treatments, respectively, without disappearance of the organisms. These were tentatively considered as fever therapy failures. However, subsequent follow-up has shown that these cases became free of organisms, when they were examined after their second and third subsequent menses, and have been free of organisms and have remained asymptomatic since.

In one case, the treatment was ceased before completion of the course, because during the induction of the fever, the patient developed repeated attacks of tetany which were refractory to all types of treatment. However, it must be stated that she was then given short-wave therapy to the pelvis. Despite this inadequate course of treatment, the organisms disappeared.

The average age incidence of these patients was 23.6 years. They all showed a definite gain in weight at the conclusion of the course of treatment. Two of the patients were subsequently reinfected by their husbands, which means that the mate must be adequately treated, if we are to establish a permanent cure. One patient who had bilateral salpingo-oophoritis prior to the onset of treatment, subsequently conceived and delivered a living normal infant. This last observation has also been made by Stafford and Warren, who have had complaints from some prostitutes, who had been sterile, but following the completed treatments of fever therapy managed to become pregnant.

We have had no experience in the use of sulfanilamide in combination with fever therapy. However, since the advent of this drug, complications due to the gonococcus have apparently been reduced, as is evidenced by the diminution in the number of patients, male or female, who have entered the hospital for the treatment of acute complications due to the gonococcus.

DR. JOHN F. KUHN, OKLAHOMA CITY, OKLA.—Sulfanilamide undoubtedly is curing and aiding in the cure of a very great number of infected persons. In this paper by Randall, Krusen and Bannick, 15 patients out of a total of 16 are reported cured, and when we consider the simplicity of its administration, we may well hope that this is the answer to our long search. Yet it is unfortunate that the drug has been exploited to the poorly informed lay-public, for it may be a very dangerous drug in lay hands.

Various strains of gonococci will probably require varying blood concentrations. Fortunately a concentration up to 9 or 10 mg. per 100 c.c. of blood will cure a very high percentage of the cases, but some more resistant strains may require much higher concentrations with resultant formation of methemoglobinemia or the causation of the grave agranulocytosis. Wendell of the Department of Biological Chem-

This group of cases is small but would seem to indicate that the percentage of patients who will have consistently negative cultures is essentially the same after sulfanilamide is employed in the treatment of gonorrheal infection as it is after fever therapy is employed. In other words, there are certain cases in which the infection will fail to respond to the administration of sulfanilamide. In this small percentage of cases a combination of fever therapy and sulfanilamide will probably result in consistently negative cultures.

TABLE III. OUTLINE AND RESULTS OF SULFANILAMIDE THERAPY IN SIXTEEN CASES

CASE	DURATION OF TREATMENT, DAYS	SULFANILAMIDE			NUMBER OF NEGATIVE CULTURES	DURATION OF FOLLOW-UP STUDY, DAYS
		TOTAL AMOUNT, GR.	AVERAGE DAILY DOSE, GR.	MG. PER 100 C.C. OF BLOOD		
1	23	1260	60	6.6	4	21
2	14	900	63+	6.1	4	21
3	11	700	63+	6.6	4	28
4	6	310	50+	6.8	4	60
5	8	430	53	6.0	4	21
6	8	430	53	6.6	4	23
7	8	400	50		5	28
8	5	250	50		4	21
9	9	450	50		2	30
10	7	280	40		3	28
11	8	520	65		2	28
12	8	430	53		4	21
13	8	430	53		4	28
14	17	880	50+		5	35
15	8	430	53		4	24
16	21	1350	64+	9.6	*	
Average	10.5	590	54+			

*Culture still positive.

It would seem from our experience that gonorrheal infections of the female genital tract should first be treated by the administration of sulfanilamide if this drug can be given under the direction of the physician. Our experience so far indicates that a large percentage of patients with gonorrhea will respond to sulfanilamide therapy alone. Certain infections will be found to be intractable to this method of treatment. When this is the case it would seem best to recommend a combination treatment with sulfanilamide and artificial fever therapy.

DISCUSSION

DR. CHARLES DRABKIN, St. Louis, Mo.—The value of fever therapy in certain diseases has been definitely established. We cannot emphasize too strongly, however, the importance of the preliminary training of the medical and nursing staffs, and the care and caution to be given to the patient before, during, and after the course of treatment. The type of machine used is not as important as the personnel operating the machine and watching the patient. This form of therapy is not adaptable to office practice. Every patient must undergo careful preliminary studies. The same contraindications exist as would make her unfit for a major surgical operation. Patients with heart disease, arteriosclerosis, hypertension, nephritis, diabetes, and tuberculosis are bad risks.

that we are not so expert in our clinical differentiation between endometriosis and inflammatory conditions of the genitalia. There was a group of cases which did not respond to this treatment that have come to operation. In 85 to 90 per cent there have not been straight inflammatory cases, but were either endometriosis or inflammatory conditions associated with endometriosis. Hence this method of treatment has come to be regarded not only as of definite therapeutic value but of diagnostic use also.

DR. HOWARD HEWITT, CHATTANOOGA, TENN.—Sulfanilamide may cause an anemia due to the fact that it may not be completely oxidized. My experience with sulfanilamide has been very disappointing. I think from now on I am going to use the intravenous method.

DR. GEORGE E. COWLES, WICHITA, KAN.—I have a patient in the hospital at the present time who, following standard doses of sulphaniilamide, developed a deficiency of white blood cells to the point where she had a white count of 600. Following that she broke out with skin lesions, so that her skin sloughed from almost the entire body. For three or four days we thought the patient was going to die. This patient has been in the hospital about a month, and now, after repeated blood transfusions, is recovering. It should be emphasized that sulfanilamide is a very dangerous drug.

DR. RANDALL (closing).—Any treatment that will accomplish symptomatic cure in inflammatory disease of the female pelvis is worthy of consideration. Sulfanilamide therapy perhaps still requires further evaluation; nevertheless we cannot ignore the data that have accumulated. The treatment should be administered under the direction of a physician just as carefully as artificial fever therapy.

ARTIFICIAL FEVER THERAPY IN PELVIC INFLAMMATORY DISEASE*

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IT IS the purpose of this report to evaluate the results of fever therapy in the treatment of forty cases of gonococcal pelvic inflammatory disease. A decade of accumulated experience has proved its value and accurate follow-up observations of treated patients attest to its specificity. Clinical responses in this series have been satisfactory and dramatically prompt.

The treatment of gonorrhea in the female has been accomplished by local tissue heating and systemic hyperpyrexia. Gurnee² feels that the combination of the Elliott machine with the fever cabinet affords the best results, a fact borne out by the work of Randall and Krusen. He also found that the combination of short-wave diathermy with the heat cabinet is likely to produce vaginal burns and sloughs. However we have found it inadvisable to combine local tissue heating with systemic hyperpyrexia. When vaginal heating is employed, the surrounding tissues are elevated to temperatures nearly approximating that of the vagina, thus preventing accurate rectal temperature recordings. Since the patient is taking iced saline continuously, mouth tem-

*Presented at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

istry and Internal Medicine of Washington University will shortly publish details of experiments dealing with intravenous methylene blue given to overcome methemoglobinemia produced by high concentration up to and above 50 mg. per 100 c.c. of blood. He has definitely proved its value and so we may overcome one of the grave dangers.

Agranulocytosis has been reported following administration of sulfanilamide. Other causative factors have, however, not been ruled out in these cases and there is still doubt as to whether it has resulted from the administration of sulfanilamide. *However, it bears watching.* Visual field defects reported have cleared up after the withdrawal of the drug.

Some complementary treatment may be necessary with the sulphanilamide therapy. Hyperpyrexia may be used when there is available a well organized team to supervise the patient and the apparatus employed. Diathermy or short wave applied and observed by an experienced operator may be worth while, but our results have been disappointing. Heat as applied by the Elliott machine has been worse than disappointing in our hands. The manipulation required of the infected tissues at such frequent intervals is certainly contrary to physiologic processes. We have discarded this method entirely. The simplest form of complementary treatment, the retention of hot normal saline enemata, has given us the best results.

DR. EARL C. SAGE, OMAHA, NEB.—Dr. A. E. Bennett and his associates at the Clarkson Hospital have treated 61 female patients in the Kettering fever cabinet, with an adequate follow-up in 54. Of these patients 19 had positive smears after treatment, and of these 19, nine had had four or more fever treatments. In other words, 17 per cent of those treated had persistently positive smears despite fairly adequate treatment. Treatments were given every third or fourth day and each treatment was of six hours' duration, at 106 or 107° F.

There were 16 women with gonorrheal arthritis, 9 of whom received complete relief, and 7 marked relief. Eleven of these arthritic patients had genital tract involvement as well, and are therefore included in the previous group. That relief of gonococcic arthritis is not inconsistent with the persistence of a genital tract infection is shown by the fact, that 5 of these 11 patients had positive smears after their arthritis had been relieved by fever therapy.

Since, in spite of the time, expense and discomfort involved in taking several six-hour fever treatments, the results were unsatisfactory in 17 per cent of the cases, these workers have recently been trying to clear up gonococcic infections with one ten-hour treatment. The results promise to be at least as satisfactory as with the old technic of repeated shorter treatments, while at the same time much less expensive and more satisfactory for the patient.

DR. RALPH LUIKART, OMAHA, NEB.—Some thermal and chemical tests have been made on cultures in vitro to determine the amount of heat needed to kill the invading bacteria. These tests seemed to be of great value. We found in some that a temperature of 110° F. was required in order to destroy the organisms. Cases that required, as the cultures showed, either a high concentration of sulfanilamide or a high temperature were given different types of treatment.

DR. FRED L. ADAIR, CHICAGO.—It seems to me a priori that infections that are accompanied by high fever reactions in the human body might be the type of infection that would respond to hyperthermia, whereas the type of infection that has a low fever reaction might not respond as favorably to high fever therapy.

The so-called Elliott treatment or local hyperthermia is a valuable method of treating local genital infections in the female. We have used two types of apparatus, one in which the treatment is administered through a hydrostatic bag and another through a superheated air bag. We have treated about 300 cases, and in 90 per cent we have had subjective cures. In a much smaller percentage of cases we have had anatomic cures.

Since starting this treatment three years ago we have followed the patients rather conscientiously for one to seven months. An interesting side light was that we found

method. Cultures were attempted in some cases but reliance on the smear was usually sufficient for diagnosis. All cases included in this series were checked by smears, either obtained by us or by the referring physician. One patient had left lower quadrant pain, tenderness and discharge with negative smears. The husband admitted a specific infection previous to marriage. Consequently, the patient was given a test treatment with improvement. However, relapses recurred after subsequent treatment and laparotomy revealed pseudomyxoma peritonei as the causal factor.

The duration of the infection before the patient sought medical aid varied from two weeks to three years. Interim treatment in some instances consisted of local chemotherapy, intragluteal milk injections or local pelvic heating, while others denied that any form of therapy had been used.

The most frequent complaints noted were bilateral or unilateral lower quadrant pain, tenderness, and vaginal discharge. Constitutional reactions occurred in direct proportion to the recency of the infection and consisted of chills, fever, and leucocytosis.

The stage of infection was classed as acute, subacute, and chronic. The types of infection were urethritis, Bartholinitis, cervicitis and salpingitis. Monoarticular or polyarticular arthritis was the most frequent complicating factor and occurred in 12 per cent of the cases.

RESULTS

Our criteria of cure is predicated on the absence of gonococci as determined by smear as well as the subsidence of symptoms. The ideal treatment for specific pelvic inflammatory disease in women might be postulated as one free from mortality, providing a cure in minimum time, leaving no sequelae, available to every woman regardless of her economic status and one which leaves the reproductive functions unimpaired. While the ideal by no means has been obtained our experience with hyperpyrexia has yielded the following results with 40 cases:

- 3 patients were cured with one treatment.
- 25 patients were cured with two treatments.
- 5 patients were cured with three or more treatments.
- 7 patients were either unable or unwilling to continue treatment until cure was effected or failure could be determined.

The longest time any patient has been observed has been three years and no patient is reported who has not been carefully examined for a period of three months following treatment. One patient required eight fever sessions before she became bacteriologically cured although she was completely asymptomatic after the third treatment.

Owing to variable factors the number of treatments necessary to effect a cure could only be determined by trial. It has been our policy whenever feasible to administer one additional treatment after the smears became negative as an added precautionary measure.

SUMMARY AND CONCLUSIONS

Fever therapy is a strenuous form of treatment and its application is attended with some risk. It is a hospital procedure and its successful use requires the services of trained personnel.

perature records are not accurate and the danger of superhyperpyrexia is always imminent. On several occasions when the combined method was used, patients appeared to be near vascular collapse although oral temperatures were only 104° F. Upon withdrawing the patient from the cabinet the temperature was found to be above 108° F. To a lesser extent, vaginal burns from vaginal diathermy have produced tissue necrosis and sloughing.

Our experience has been with the heated humidified cabinet previously described.¹ It cannot be too frequently emphasized that the apparatus used for fever production is of relatively minor importance compared to the care and caution that should be used in administering the treatment. An efficient fever therapy department requires a physician trained and interested in the use of fever, consultants in the various specialties alive to its possibilities, well trained nurse technicians and finally the fever apparatus.

Before subjecting a patient to treatment she is studied with the same care and caution she would receive were she a candidate for a major surgical procedure. A complete clinical survey is made and special chest and cardiac examinations are carried out. It is well to exclude from treatment all patients past the age of 45 and all subjects with evidences of cardiovascular incompetence.

On the morning of treatment breakfast is omitted and 1.5 to 3 gr. of sodium pentobarbital are administered orally. The patient is completely disrobed and placed in a preheated fever cabinet, the arrangement being such that the head and neck are in the open. The patient's body is freely accessible through doors in the sides of the cabinet. The patient lies on a comfortable rubber mattress, the body being encased in blankets.

Heat and humidity are supplied by a thermostatically controlled electrical unit. The maximum temperature of the cabinet approximates 130° F. and an atmosphere of 40 to 50 per cent humidity is maintained. The body temperature is raised at the rate of approximately one degree every fifteen minutes until the desired temperature is attained (106° to 107° F.). When 102° F. is reached one-third of a grain of pantopon is usually administered. An ice cap is placed on the head and a fan circulates the air about the head. Iced saline solution amounting to many liters may be consumed during the treatment. Rectal temperature, pulse, respiration, and blood pressure readings are recorded every ten to fifteen minutes. The body temperature is maintained between 106° and 107° F. for five to six continuous hours. The treatments are repeated every three to five days until the desired result is obtained.

Complications occasionally noted are facial herpes, nausea and vomiting, headache and to a lesser extent general erythema and tetany. Impending cardiovascular collapse is indicated by a pulse rate of more than 160 beats per minute, and treatment should be discontinued immediately when this situation arises.

The ages in our series varied from fourteen to fifty, the average being twenty-eight years. This corresponds to the period of the most active sexual life of the female and incidentally is an age which permits strenuous treatment with relative safety. The oldest patient exhibited a concomitant polyarticular periartthritis and arthritis as well as evidence of gonorrheal ophthalmia.

In more than 90 per cent of our patients a history of contact was established, over 80 per cent of them being married. It was definitely established in most instances that infection came from the husband.

Cervical and urethral smears were examined by the gram method and by methylene blue stain. Eighty per cent of our cases showed the presence of gram-negative intracellular diplococci, morphologically *Neisseria gonorrhoeae*. The older the infection the less frequent was a positive slide obtained. Interestingly enough the methylene blue stain in our hands was as accurate diagnostically as the Gram

action upon the eighth nerve. The evidence is also quite conclusive that quinine is carried through the placental circulation and reaches the fetus in high concentrations.^{3, 4} Covell has proved that quinine, given to parturient guinea pigs, in poisonous doses, produces demonstrable changes in the auditory apparatus of the offspring.⁵

Great clinical interest has been aroused among the otologists by the publications of H. Marshall Taylor who, in writing upon this subject, made the following statement: "Despite the fact that modern textbooks on otology point out the selective action certain drugs have for the auditory apparatus, otologists have virtually ignored the possible damage to the ear of the fetus which these drugs may cause when administered to the pregnant woman. That quinine, the salicylates and alcohol can have a permanent influence on the auditory nerve and that quinine in particular has a predilection for this nerve are established facts."¹

In another publication, Taylor reported 5 cases of complete deafness in children three to five years of age whose mothers were given massive doses of quinine during or before parturition for malaria, attempted abortion, or induction of labor.⁶

In a recent study, Heider reported that in the southern states, particularly Florida and Alabama, two and one-half times more deaf children are born in the second half of the year, corresponding to the seasonal prevalence of malaria.

Degenerative changes in the mechanism of the ear, due to quinine, salicylates, and alcohol, have been reported by Wittmarck,⁷ Bernard and Daniels⁸ and others.

METHOD

These experiments were carried out upon rabbits. A series of twelve animals in all was studied. The first animal was given $\frac{1}{2}$ gr. of quinine bisulphate by mouth each day for ten days, i.e., 5 gr., previous to autopsy. This was done in order to note the effect of massive doses upon the auditory apparatus of the individual animal. The remaining eleven were animals from three different litters; the mother of Animals 2, 3, and 4 receiving 5 gr. of quinine bisulphate; the mother of Animals 5 and 6 receiving 3 gr.; the mother of Animals 7, 8, 9, 10, 11, and 12 receiving 1 gr. This latter was regarded as being the equivalent of the average therapeutic dosage given to parturient women for the purpose of inducing or stimulating labor, i.e., 15 gr. to parturient women, and 1 gr. to an 8 pound animal, or approximately 16 mg. per kilogram of body weight. The Animals 2 and 12 were autopsied at the age of two months.

The drug was administered by mouth in each instance in order to simulate as nearly as possible actual clinical conditions. With each series of animals autopsied, an animal from a control litter was studied. The control animals were bred, reared, and cared for under absolutely identical conditions to those of the experimental animals. This was done in order to rule out any chronic hereditary or environmental disease which might affect the animals in any manner.

TECHNIC

The material of the control animals and Animal 1 consisted of the auditory nerves alone. The rabbits were killed with chloroform and the nerves were removed immediately after death. The material was preserved in formalin, and also in Mueller's solution. The nerves preserved in formalin were stained by the Spielmeier Method (myelin sheaths) while the tissue preserved in Mueller's solution was stained by the Marchi Method (osmic acid stain of degenerative fat granules).

From Animals 7, 8, 9, 10, 11, and 12 (1 gr. of quinine via the placental circulation), the petrous pyramid was removed immediately after death and the method of Eckert-Moebius (*Handbuch der Hals-Nasen und Ohrenkrankheiten*) was employed. It consisted of the following procedures: (1) Wittmaak's fluid for fixation: Pot. bichrom. 5 per cent, 50 c.c.; formalin, 10 c.c.; glacial acetic acid, 5 c.c.; Aq. dest. to 100 c.c. The specimens remained three weeks in this fluid. (2) Decalcification: Nitric acid, 5 c.c.; formalin, 5 c.c.; Aq. dest., 100 c.c. The solution was changed every 3 days. The tissue remained three weeks in this decalcifying solution.

Complete cure may be expected in upwards of 80 per cent of cases where three or more treatments are administered, providing the body temperature is maintained at 106° to 107° F. for five to six hours per treatment.

The acute stage of the infection is no contraindication to the use of fever therapy. In fact, the more acute the symptoms, the more dramatic will be the result.

Repeated clinical examinations following treatment indicate that the functions of the female reproductive tract are not essentially altered.

Should fever therapy fail to effect a cure the patient could readily undergo any other form of treatment deemed advisable.

The results obtained in treating 40 patients with specific pelvic inflammatory disease by hyperpyrexia, have convinced us of its efficacy and stimulated our interest in its continued application.

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EFFECT OF QUININE UPON AUDITORY NERVE*

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IT HAS been estimated that of the 10,000,000 deaf persons in the United States, 3,000,000 are children.¹ A committee engaged in a statistical study of the children in public schools for the deaf, stated that of 3,334 children studied, 62 per cent were congenitally deaf.²

This statement, in years past, would probably have held little or no interest for obstetricians. The medical literature of the world, however, is gradually accumulating evidence which, although not conclusive, may place a great share of the responsibility for this army of defective individuals upon men who care for women during their period of reproductivity. The effect on the fetus of drugs administered to the maternal organism has long been a problem of interest and at present there are three of principal importance, i.e., alcohol, salicylates, and quinine.

This investigation was undertaken for the purpose of determining the histopathologic effect of quinine administered to the fetus in therapeutic doses via the placental circulation.

REVIEW OF LITERATURE

In this review of literature the attempt was not made to cover completely all of the points involved, particularly those which have to do with definitely established facts, for instance the literature is replete with evidence that quinine has a selective

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the Spielmeyer stain. We see degenerated myelin sheaths appearing as whitish gray spots. In Figs. 4, 5, and 6 we were able to examine the spirale ganglion (Fig. 4), the auditory and vestibular nerve (Fig. 5) and the peripheral neuron of the cochlear nerve (Fig. 6). Please remember that this is material from the important Litter 3; important because this litter received 1 gr. quinine bisulphate in utero, cor-

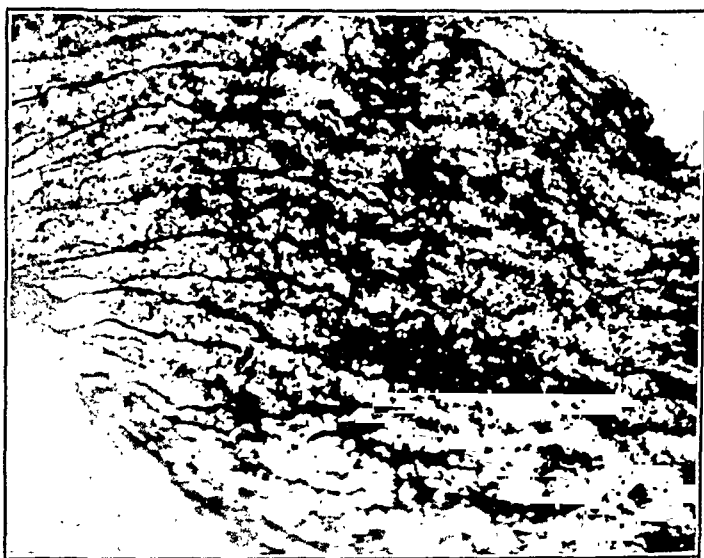


Fig. 3.—Same nerve shown in Fig. 2 stained by Spielmeyer method. Degenerated areas shown as whitish-gray spots.

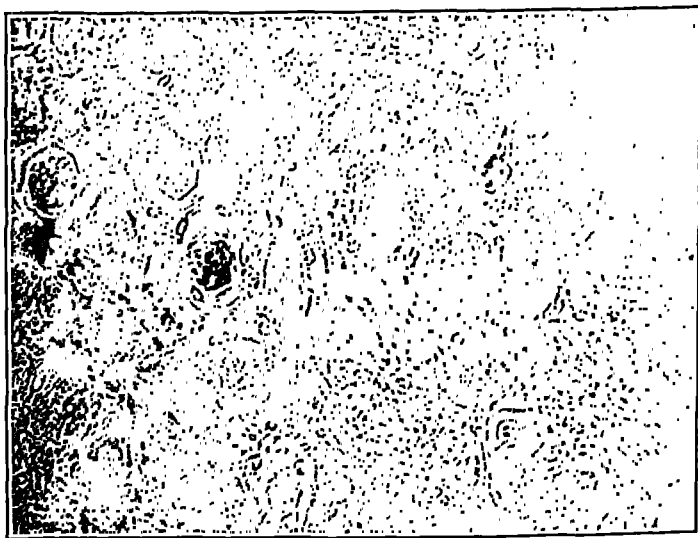


Fig. 4.—Spirale ganglion from Litter 3. Marchi stain. Many degenerated ganglion cells with fatty globules in the cytoplasm.

responding to the therapeutic dose given ordinarily to parturient women. The spirale ganglion showed marked degenerative changes. Many ganglion cells showed destruction of the nuclear substance, condensation of the cytoplasmic structures, and fatty degeneration of the cytoplasm. There is some round cell infiltration of the stroma of the ganglion. Many cells were shrunken and without definite structure.

(3) 5 per cent Sod. sulphate for twenty-four hours. (4) Running water twenty-four hours. (5) After cutting the petrous bones into three parts, the following osmic acid stain was used, for 8 days: Osmic acid 2 per cent, 5 c.c.; Pot. bichrom. 5 per cent, 5 c.c.; Glac. acetic acid, 1 c.c.; Aq. dest., 10 c.c. (6) Running water for twenty-four hours. (7) Embedding in celloidin: 70 per cent alcohol, 1 day; 95 per cent alcohol, 1 day; Absol. alcohol, 1 day; thin celloidin, 2 weeks; medium celloidin, 4 days; thick celloidin, 2 days.

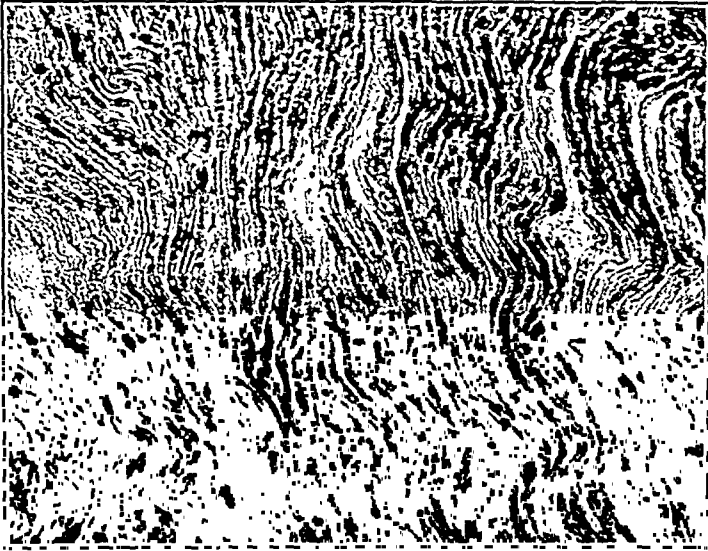


Fig. 1.—Normal auditory nerve. Marchi stain.

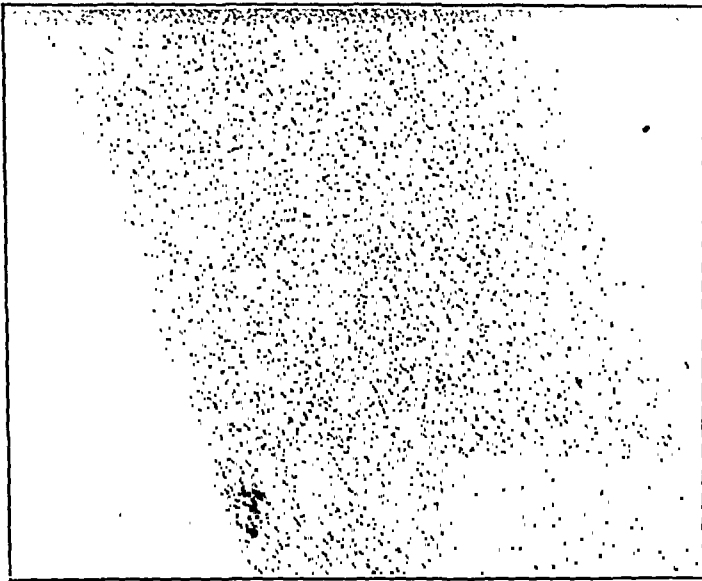


Fig. 2.—Rabbit's auditory nerve after receiving quinine. Marchi stain. Every fiber contains minute black granules of degenerated myelin. (Animal 1.)

DISCUSSION

The auditory nerves in the control animals stained with the Marchi stain show only occasional black granules (Fig. 1). In the material obtained from Animal 1, receiving 5 gr. of quinine bisulphate by direct administration, every fiber contains minute black granules of degenerated fat globules (Fig. 2). Fig. 3 shows the same nerve stained by

quinine, since the degeneration in the ganglion appears to be less severe than that of the nerve fibers.

SUMMARY

As stated previously, this work was undertaken for the purpose of determining histologically the effect on experimental animals of dosages of quinine bisulphate given in utero corresponding to the dosage received by parturient women for the purpose of inducing or stimulating labor.

These experiments show rather conclusively that small doses of quinine do produce definite destructive changes in animals. The question now naturally arises, what is the inference to be drawn clinically? The otologists are certain that complete deafness is likely to occur in individuals receiving massive doses of quinine in utero. If this is true, are we not justified in assuming that slight degenerative changes produced by smaller doses might be responsible for a great many of the auditory defects which develop in young or young adult individuals?

Many obstetricians tell us that no untoward effects have been observed in the use of quinine over long periods of years. This statement is open to question, however, because the obstetrician often times loses sight of these patients after a few years, and the hearing defects are not called to his attention or the history of quinine administered during parturition may have been overlooked. Some investigators believe that auditory defects occur only in individuals who have an idiosyncrasy to quinine. This conclusion is not borne out by our experiments because every individual of each litter of animals showed the same degenerative changes in the auditory nerve.

Now we all of course realize the impossibility of drawing definite clinical conclusions from animal experimentation. It would seem, however, that enough evidence is at hand to warrant intensive clinical study by obstetricians as well as otologists. This can best be brought about by a very careful scrutiny of the natal and prenatal history of every individual showing hearing defects, to determine whether or not quinine or other drugs were administered in utero. In the meantime, until conclusive evidence is accumulated to prove or disprove this problem, the author is of the opinion that quinine, the oxytocic value of which has always been problematical,⁹ had best be omitted from the obstetric armamentarium because we cannot be certain that we are not bringing about great harm to future generations.

CONCLUSIONS

1. Review of the literature proved that quinine bisulphate has a selective action on the eighth nerve.

2. Strong evidence was found in the literature which tends to prove that quinine, in massive doses, administered in utero produces hearing defects.

In Fig. 5, we see the auditory and the vestibular nerve stained by the Marchi method in which marked degeneration is found in the auditory nerve with a very slight degeneration found in the vestibular nerve. In Fig. 6, we find the cochlea with the organ of Corti did not show pathologic changes. We did not find any hemorrhages or degenerative changes in the structure as some otologists believe. The periph-



Fig. 5.—Marchi stain of cochlear and vestibular nerve. Black granules of fatty degeneration myelin in lower nerve (cochlear nerve), Litter 3.



Fig. 6.—Peripheral neuron of cochlear nerve. Black granules of osmic acid stained fat in nerve fibers. Litter 3.

eral neuron of the cochlear nerve, however, again showed marked degenerative changes, i.e., fat globules stained with osmic acid.

Whether the lesions in the spirale ganglion are primary and those in the neurons and axons of the cochlear nerve are secondary, is difficult to decide from our histological findings. It seems more likely that the myelinated nerves are affected first by the toxic effect of the

means have been as satisfactory and probably even more so than when quinine is used. There is rather definite reason to believe that quinine is decidedly damaging to the fetus.

DR. WILLARD R. COOKE, GALVESTON, TEX.—I am able to report three cases of so-called congenital deafness in children whose mothers had quinine for the induction of labor (15 to 30 gr.). Whether this had anything to do with the deafness we do not know. On the other hand, I have had no opportunity to treat malaria, because it does not occur in Galveston. I have seen only three cases of malaria complicating pregnancy, and in two of these the children were perfectly normal in hearing. In one case the mother has estivo-autumnal malaria which was very resistant to quinine; ultimately she received 90 gr. a day by injection and mouth over a period of seven weeks. This baby, as well as we could determine, seemed to be more or less deaf for about six months; but ultimately the condition cleared up and he is now, at seventeen months, perfectly normal in hearing. This brings up the question of the possible regeneration of the nerve if the nerve was really damaged by the quinine.

There was a point not brought up which should be, since we are talking about quinine; that is, the suggestion that fetal death may be caused by quinine, as brought to our attention by Dr. King several years ago. I have had two definite and one probable cases of fetal death from this cause. When at the height of quinine intoxication (as indicated in the mother by deafness and tinnitus) the baby begins to move violently and suddenly becomes and remains still with disappearance of the fetal heart sounds, we have suggestive evidence that quinine may cause death of the unborn infant. Since quinine does not have any material effect as an oxytocic in strengthening the contractions, and may be dangerous to the fetus, its use in obstetrics should be discouraged. I should like to see experiments carried out on another series of animals with the view of establishing quinine as a possible cause of fetal death.

Fränkel, W. K.: *Urethral Inflammations and Strictures in Women*, Wien. klin. Wehnschr. 48: 1463, 1936.

In spite of its easy accessibility lesions of the female urethra are often overlooked. The bladder is frequently incorrectly treated when treatment should be directed towards the urethra. Seemingly functional bladder disturbances may be caused by inflammatory urethral changes. Skene's glands infections and gonorrhea in the female are essentially diseases of the urethra. Only in rare cases does gonorrheal urethritis give rise to a cystitis. Urethritis may occur in acute infectious diseases such as diphtheria and scarlatina and may also follow focal infections. Inflammatory changes in the urethra do not merely produce pain in the urethra but may give rise to pain higher in the urinary tract viz.; bladder, ureters, and kidneys.

If simple methods of diagnosis fail, the urethrocytoscope must be used. The therapy of urethritis is fairly simple; alkalization of the urine with sodium bicarbonate is worth while. This treatment removes the effect of acid irritating urine; while this may be given by mouth, local applications of iodine-silver-gelatin may be used in the urethra. Bladder irrigations may be given with various mild irrigants. Prophylactically reinfection should be avoided and dietotherapy should be carried out. Urethral strictures must be looked for and treated; the urethra may be dilated with a soft rubber catheter or small Hegar dilator; diathermy may also be employed. These treatments are carried out under local anesthesia. If syphilis is a factor, this should of course be treated by established methods.

W.S.B. SERBIN.

3. Quinine bisulphate, administered to individual animals in massive doses produced myelin sheath degeneration of the auditory nerve.

4. This investigation shows that quinine bisulphate, administered in utero in therapeutic doses produces degeneration in the auditory nerve, spirale ganglion, and peripheral neuron.

5. With this evidence at hand, intensive clinical investigation is urged to determine whether or not therapeutic doses of quinine bisulphate, administered clinically, will show the same effects.

I wish to acknowledge the valuable assistance of Dr. C. A. Hellwig, Chief of the Department of Pathology, at St. Francis Hospital, Wichita, Kansas, for the technical work and pathologic reports on this material.

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DISCUSSION

DR. MINNIE L. MAFFETT, DALLAS, TEX.—Such careful studies as those of the essayist, as well as of King, Taylor, and others render the possibility of fetal deafness from quinine one that the obstetrician must take most seriously. Probably all obstetricians are agreed that quinine in the induction of labor, or even for the augmentation of uterine contractions during labor, is of little use. Many other methods now available are certainly more rational and dependable. I, therefore, believe that the use of quinine in the attempted induction of labor should be entirely discontinued as long as it is on trial as an etiological factor in deafness.

The internist or general practitioner, however, has another problem. A severe case of malaria must, after all, receive treatment by some recognized method, quinine, plasmochin, atabrine, etc. While the last two are without effect on the auditory nerve, their toxicity in other directions cannot be overlooked. Regardless of this fact, however, some one of them must, of necessity, be used as treatment for malaria complicating pregnancy.

If quinine is as provocative of congenital deafness as these studies would indicate, one wonders what must have been the frequency of deafness in malaria districts during past years when this disease was much more prevalent than at the present time. It would be of interest if comparative statistics could be made available contrasting the conditions existing in the malarial and nonmalarial sections of the country.

Regardless of Fall's statement that quinine is of low toxicity and that as much as 600 gr. have been given to a patient within twenty-four hours without any disturbance, it is still evident that there is a wide variation in the idiosyncrasy of individual persons to this drug. Inasmuch as the placenta undoubtedly does not serve as a barrier against the transmission of the drug to the fetus it would seem evident that a high threshold of tolerance in the mother is no safeguard to possible damage to the auditory mechanism of the fetus. Deafness may unfortunately not be discovered until the child is of school age.

DR. J. W. REDDOCK, NEW ORLEANS, LA.—In the last few years we have discontinued the use of quinine in the induction of labor. It was my opportunity to carry out a series of inductions using rupture of the membranes in an effort to induce labor without the use of quinine. The results of the induction of labor by this

Pulmonary Tuberculosis.—Among the patients with pulmonary tuberculosis who were sterilized, 79 per cent were done by the abdominal route and 21 per cent by the vaginal route. The majority of the abdominal cases were done in the early part of the period under consideration. There is no intention to enter into a detailed discussion of the methods of delivery, but experience has shown that it is safer for some of these patients to be delivered vaginally, assisted by sedation, low forceps and episiotomy, and subsequently to be sterilized by the vaginal route. It is felt that active pulmonary tuberculosis is an indication for sterilization in almost every instance, especially in the indolent and ignorant class of patients¹² who cannot be relied upon to carry out contraceptive measures. Cesarean section is indicated when the condition is in a far advanced stage, as in patients with artificial pneumothorax, where long labor is expected (as in a primipara).

Although the average medical consultant is prone to advise cesarean section in tuberculous patients, our experience has shown that abdominal section is much more hazardous for these patients than is a delivery through the natural passages with elimination of the second stage of labor.

Tuberculosis of Spine.—The two cases listed as tuberculosis of the spine were sterilized primarily for reasons listed under other classifications and therefore will not be discussed here.

Toxemias of Pregnancy.—Under the heading of toxemias of pregnancy, three general types are included: (1) pre-eclamptic, (2) nephritic, and (3) eclamptic. The information concerning previous pregnancies given in the histories was not sufficient in every instance to differentiate the pre-eclamptic from the nephritic. Of the 28 patients with toxemia, 12 had cesarean section, 3 had associated abdominal operations, and 4 had hysterotomy. The latter 4 had nephritic toxemia, did not improve under treatment, and therefore required interruption of pregnancy (it has been the routine in such cases to do an hysterotomy with sterilization at the same time; this procedure has seemed safer in the majority of cases than the induction of abortion, followed at a later date by sterilization). Nine of the 12 patients who had cesarean sections had indications which, combined with the toxemia, made abdominal delivery necessary; the other 3 patients should have been delivered through the normal passages and subsequently sterilized vaginally. Nine patients with toxemia had vaginal sterilization, the preferable method.

It seems to be generally agreed that patients with nephritic toxemia should be sterilized. The authors are of the opinion that patients with eclamptic toxemia should also be sterilized, since the incidence of nephritis following the toxemia in these patients is exceedingly high.⁹ These sterilizations should be carried out by the abdominal route only where other attendant conditions make this method imperative.

Cardiac Lesions.—Cardiac patients who stand up well under a physical strain should be delivered vaginally. The question of whether or not cardiac patients have more rapid and easier labors than do normal patients seems to be a debatable one, with apparently good evidence on both sides. Corwin and co-workers state that "cardiac cases have as a rule easy labors."³ Daly remarks that "labor is usually shorter and less strenuous in cardiacs and . . . is a factor that can be controlled by good obstetrics."⁴ MacLennan considers it "of considerable importance to note that labor in a patient suffering from cardiac disease is frequently short and precipitate."⁵ On the other hand, Nelson and Eades, basing their observations on 530 cases of organic heart disease, do not find that cardiac patients have shorter or easier labor than normal women.¹⁰

The authors are inclined to agree with those investigators who maintain that labor is less strenuous and shorter in cardiac cases. On this basis, 62 per cent of the cardiac patients in this study were delivered through the natural passages and subsequently sterilized vaginally. In 38 per cent the following complications made other methods advisable: one patient had mitral stenosis and insufficiency with threatened heart failure; another had rheumatic heart disease, complete heart block and toxemia of pregnancy. It was felt that neither of these two patients could undergo labor and that cesarean section was therefore indicated. A third patient was delivered vaginally, with the intention of sterilizing vaginally, but an old pelvic inflammatory disease made this impossible. The fourth patient should have been delivered and

STERILIZATION OF OBSTETRIC PATIENTS IN VANDERBILT UNIVERSITY HOSPITAL 1925-1937*

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of Medicine)

A STUDY of 100 obstetric cases sterilized in Vanderbilt University Hospital from October, 1925 to March, 1937 is the basis for this paper. All the patients were sterilized by operations on the Fallopian tubes, the abdominal approach being used in some instances and the vaginal approach, in others. The indications for sterilization are divided into eleven groups, and the cases will be discussed under their particular classifications.

Of the 100 cases reviewed in this report, 71 patients were sterilized by the abdominal route and 29 by the vaginal route. It has been concluded within the last five years that the vaginal method should be used whenever possible. In this period, that is, within the last five years, 33.4 per cent of the sterilizations have been vaginal. This is in sharp contrast to the sterilizations for the first half of the period of study, when only 10.5 per cent were done by the vaginal method.

There is considerable overlap in the indications for sterilization. For example, one tuberculous patient was feeble-minded and epileptic. Another tuberculous patient had a funnel pelvis. Such cases were listed under the classification of tuberculosis as well as in other groups.

It must be remembered that one indication alone may not be sufficient cause for sterilization but that, considered with other indications, it does warrant sterilization. Likewise, in many instances, a condition might indicate vaginal sterilization, where a combination of conditions would make abdominal sterilization advisable.

TABLE I. STERILIZATION—INDICATIONS AND METHODS

INDICATION	NUMBER OF STERILIZATIONS		
	ABDOMINAL METHOD	VAGINAL METHOD	TOTAL
Pulmonary tuberculosis	23	6	29
Tuberculosis of spine	2	0	2
Toxemia of pregnancy	19	9	28
Cardiac lesions	6	10	16
Diabetes	2	1	3
Pelvic deformities	8	0	8
Abnormalities of the soft parts	5	0	5
Previous cesarean sections	11	0	11
Social and economic conditions	1	2	3
Request of patient	3	2	5
Miscellaneous	4	0	4

*Read at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

abdominally in association with suspension of the uterus. The vaginal sterilizations were requested because of multiparity in one instance and a previous long, difficult labor in another.

Whether or not sterilization should be done simply because the patient requests it is a debatable question. In private patients the responsibility for the decision rests with the attending physician. The attitude of the Department of Obstetrics and Gynecology of Vanderbilt University Hospital is that in charity patients all phases, social, economic and psychologic, should be considered carefully before sterilization is carried out solely on the basis of the patient's request.

Miscellaneous.—There were 4 patients who did not fall in the above classifications. In studying the history, no reason could be found for sterilization in one case. Two patients had complete laceration of the perineum which had been repaired. One patient had a large ventral hernia. These four sterilizations were carried out by the abdominal route in association with an operation for suspension of the uterus.

OPERATIVE PROCEDURE

For sterilization, almost every known technique on the tubes has been used. Most of the operations were done by the Madlener-Walthard technique (crushing, ligation with nonabsorbable suture, and partial excision of the tube). Recently, however, the Pomeroy-Lull technique (ligation with absorbable suture and partial excision of the tube) has become the method of choice.

For the vaginal sterilizations reported in this study, the following procedure of operation was adopted.¹ The patient is placed in position and the usual preparation carried out. Up to the past year, the exaggerated lithotomy position was used; recently, however, the knee-chest position has been used, since in some instances it gives better access to the tubes. After a 1 to 1½ inch incision is made into the cul-de-sac of Douglas, the operation is done according to one of the techniques mentioned above. The peritoneum and vaginal mucosa are then closed in layers with plain catgut.

After the vaginal operation, the patient is propped up in bed at the end of twenty-four hours, placed in a chair at the end of forty-eight hours, and allowed to leave the hospital four to five days from the time of operation.

EFFECTS OF STERILIZATION

Discussion of the effects of sterilization upon the sex life of the woman is frequently found in the literature. However, clinical experience has shown that sterilization per se has no effect upon the sex reaction of most women. When a change in libido does occur, it is frequently increased rather than decreased. This is probably the result of the removal of the inhibitions due to the fear of pregnancy.

FOLLOW-UP OF CASES

Of the 100 patients sterilized by operations on the tubes, 89 have either been seen personally or have responded to a questionnaire sent them. Pregnancy has not occurred in any of these 89 patients. Five patients did not reply to the questionnaire and could not be found.

sterilized by the vaginal route. Hysterotomy and abdominal sterilization were done on two patients with hypertensive cardiovascular disease who could not go to term.

Diabetes.—In diabetic patients, sterilization should be strongly considered when the disease has been particularly difficult to control, when pregnancy aggravates the condition, or when both patient and husband are diabetic. Many authorities go so far as to say that in *all* diabetic patients further childbearing is contraindicated.^{6, 7} The babies of diabetic mothers usually become very large and die ante partum. For this reason cesarean section is frequently necessary to save the baby, as was true in two of our cases. The third patient had a mild diabetes, had a small baby, and therefore was delivered and sterilized vaginally.

Pelvic Deformities.—Eight patients in our series had pelvic deformities. Of these, two had narrow, flat pelves, and both had had previous sections. One patient had a funnel pelvis and pulmonary tuberculosis. Five patients had generally contracted pelves (three had had previous sections, one was an imbecile and one was a rachitic dwarf with toxemia of pregnancy). In all these cases pelvic deformities, plus other conditions, made cesarean section and abdominal sterilization imperative.

Abnormalities of the Soft Parts.—Cesarean section was the only possible method of delivery of the 5 patients classified under the heading abnormalities of the soft parts. Other complications made sterilization necessary. Briefly, these cases were: one patient with double vagina, very large baby, previous section and requested sterilization. One patient had postoperative cervical scarring and pre-eclamptic toxemia. A third patient was obese, had stricture of the vagina, umbilical hernia repair and requested sterilization. A fourth patient had marked varicosities of the vulva, a brain tumor and tuberculosis. The fifth patient had marked varicosities of the vulva, had several children, and requested sterilization.

Previous Cesarean Sections.—"Once a cesarean, always a cesarean" has many advocates. However, "when the first was done for some reason such as placenta previa which does not exist in a subsequent pregnancy, and when her convalescence from the cesarean section was normal, the matter of permitting this patient to enter labor and deliver naturally must be entertained."¹³ The patient should be followed carefully throughout subsequent labors and if, at any time, there seems to be an impending rupture of the uterus, section should be done. In 10 of our cases of abdominal sterilization which had had previous section, the condition for which the section was done still existed: among these conditions were deformities of the soft parts and pelvis, toxemias, and threatened rupture of the uterus. The other patient requested sterilization; she probably should have been delivered naturally and sterilized vaginally. It seems to be the general opinion that the third and fourth cesarean sections should be accompanied by sterilization.

Psychiatric Conditions.—The defense of eugenical sterilization seems based on the arguments that conditions such as insanity, feeble-mindedness and epilepsy are increasing; that these conditions are mainly hereditary; and that such defective people propagate at a greater rate than does the normal population.² Feeble-minded and epileptic patients comprised by far the majority of the patients sterilized by us for psychiatric conditions. The remainder had anxiety neuroses, in which the fear of pregnancy was the outstanding symptom. Seven patients were sterilized vaginally. Nine patients were sterilized abdominally; of these, 5 patients had associated eclampsia, abnormalities of the pelvis or tuberculosis. The remaining 4 patients were imbeciles; it was felt that they could not be relied upon to carry out contraceptive measures, and they, therefore, had cesarean section and abdominal sterilization. All the sterilizations in this group were done in consultation with a psychiatrist.

Social and Economic Conditions.—Three patients were sterilized because of social and economic conditions. These conditions included deaf mutism of the patient, mental deficiency of the patient's husband, and blindness of both patient and husband.

Request of the Patient.—There were 5 patients who were sterilized at their own request. One had had two previous sections which, as has been stated, is in itself generally considered an indication for section and sterilization. One patient had had 11 previous pregnancies, the last being terminated by cesarean section on account of placenta previa. One patient had had 5 previous pregnancies and was sterilized

Clellan has brought out, while a small indication might not be reason enough to operate on an individual a combination of several will definitely indicate operation. We have now, as you well know, a proper management of diabetes and we can well permit a woman who desires children to have them.

DR. W. WORTHAM MAXWELL, SAN ANTONIO, TEXAS.—As a resident at Vanderbilt Hospital ten years ago, I operated upon one of these patients—a patient with active tuberculosis on whom we did a classical cesarean section with sterilization under spinal anesthesia. She lived about eight weeks, recovering entirely from the operation but died of a tuberculous pneumonia. The autopsy revealed several interesting features. The uterus had receded normally to the resting state; the omentum had attached itself along the site of the uterine incision and to each cornu where the medial portion of the tube had been resected. There were no other adhesions, thereby demonstrating how completely nature repairs our operative interference even in the presence of an extensive active tuberculosis.

DR. FREDERICK H. FALLS, CHICAGO.—In opening the peritoneal cavity through the vagina, we use *local anesthesia*, make an incision and proceed as if one were doing a Watkins-Wertheim interposition operation. This gives the advantage in many of these cases of finishing the operation by sewing the uterus anteriorly, thus giving support to the bladder and producing a cure of the associated cystocele which is so often present.

Sometimes these vaginal sterilization operations are unsuccessful. We had a rather interesting experience in this regard. A woman became pregnant after a Watkins-Wertheim interposition operation had been done by a gynecologist. She entered our clinic, and we were at a loss to know how to handle the situation. She had severe pain and was unable to void. I went in from below again, undid the Watkins-Wertheim interposition and pushed the uterus up into the abdominal cavity. At a later date I did a cesarean section and sterilization.

DR. LUCIUS E. BURCH (closing).—I desire to stress further the simplicity of vaginal sterilization. Recently we have placed the patient in the knee-chest position instead of the dorsal position for this procedure, which gives an easy access to the appendages. I should like also to emphasize the importance of not making traction on the tubes for the reason that it is likely to produce a tear of the mesosalpinx. The ovary should be found first, traction made upon it and then the tube will come down.

The operation as a rule is carried out under local anesthesia. We have not used the anterior method of sterilization unless hysterotomy was carried out at the same time. The anterior method of approach adds to the difficulty of the operation and the dissecting up of the bladder is time-consuming.

In regard to the efficiency of our technique of tying off the tube, our statistics are not worth much because they are too few in number. We are now using the Lull-Pomeroy technique. In other institutions where there has been a large series of cases, this technique has been successful, although there has been one recent report of a case of extrauterine pregnancy that followed the Lull-Pomeroy technique.

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Six patients were found to have died in the twelve-year period. Some 5 or 6 cases included in the study are perhaps too recent to be considered as good material upon which to base any justifiable conclusion as to the efficacy of any method.

CONCLUSIONS

In conclusion, all operations for sterilization should be done only after a careful consideration of the condition of the patient with regard to congenital or acquired defects of the parturient passages, pathologic lesions of organs or systems of organs, and abnormal mental states. The social and economic factors should also be considered.

The vaginal approach for operations on the tubes is emphasized because of (1) the ease with which it may be carried out, (2) the minimal amount of discomfort to the patient, (3) its adaptability to any type of anesthesia, especially local combined with analgesia; (4) the greatly lessened risk to the patient of infection, since the greater peritoneal cavity is not opened, and (5) the short hospitalization necessary.

The Pomeroy-Lull method is advised, both in the abdominal and vaginal approach, because of its simplicity and effectiveness, as evidenced by results here and elsewhere.⁵

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DISCUSSION

DR. S. B. HINKLE, LITTLE ROCK, ARK.—Economic indications for sterilization are brought to us conscientiously and often by people, who have only the present economic situation in mind. It would be hard for me to accept as a reason for sterilization that the present economic condition in a particular family would not warrant future childbearing. It would, however, be acceptable if the economic conditions were permanent, as when due to irremediable disabilities, for instance, blindness, deafness, feeble-mindedness.

These essayists have, I am sure, given the opinion of this entire Association when they say that the request for sterilization may be made by an individual, but the reason must be evaluated by the surgeon.

DR. A. F. LASH, CHICAGO.—Since sterilization is an operation of choice we must be very certain that in performing it our mortality is practically nil. The combination of morphine and scopolamine with local anesthesia practically eliminates the anesthetic risk.

We do not think that toxemias of the pre-eclamptic type are necessarily an indication. Chronic nephritis, however, is definitely an indication to us. As Dr. Mc-

TABLE II. INCIDENCE OF PREMATUREITY, FETAL AND MATERNAL MORTALITY, HEMORRHAGE, AND MORBIDITY

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Premature delivery (prior to 36th week)	4.4%	13.5%	19.6%
Gross fetal mortality	4.0%	7.9%	7.8%
Gross maternal mortality	0.0	0.4%	3.9%
Post-partum hemorrhage	2.6%	3.4%	5.8%
Febrile morbidity excluding cesarean sections	5.3%	5.1%	5.8%

Table II shows that the incidence of prematurity increases with age and that factor alone might account for the second row of figures showing an increase in fetal mortality; because when the gross fetal mortality is broken down into unavoidable and obstetric, the increase is found in the unavoidable group as shown in Table V.

TABLE III. PRESENTATION AND TYPE OF DELIVERY

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Spontaneous and low forceps deliveries	89.0%	69.0%	52.9%
Other deliveries	11.0%	31.0%	47.1%
Placenta previa	0.3%	0.4%	1.9%
Presentations:			
Anterior cephalic	80.6%	62.0%	49.2%
Posterior cephalic	10.4%	25.0%	27.4%
Breech and others	7.0%	5.0%	11.7%
Not stated	2.0%	8.0%	11.7%

Table III shows that malpresentations increase, which in turn leads to an increase in operative delivery. Why there should be more posterior cephalics, more breech presentations and other odd positions of the fetus among older primiparas, it is not possible to state.

TABLE IV. REASONS FOR CESAREAN

25 YR. OLD	35-39 YR. OLD	40 YR. AND OVER
1 Chronic nephritis	15 Toxemia	3 Toxemia
2 Toxemia	8 Fibroids	2 Test of labor
1 Breech with test of labor	3 Uncomplicated	2 Breech uncomplicated
1 Retinitis Pigmentosa	5 Complicated by other conditions	2 Transverse
1 Placenta previa	2 Breech uncomplicated	2 Fibroids
	11 Test of labor	1 Placenta previa
	1 Cardiac disease	3 Elective
	4 Elective	

TABLE V.

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Gross fetal mortality	4.0%	7.9%	7.8%
Unavoidable deaths	2.0%	5.4%	5.8%
Obstetric deaths	2.0%	2.5%	1.9%

A STUDY OF 288 PRIMIPARAS OVER THE AGE OF 35 COMPARED WITH 300 PRIMIPARAS UNDER THE AGE OF 25*

CHARLES EDWIN GALLOWAY, B.S., M.D., F.A.C.S., AND
TOM D. PAUL, M.D., EVANSTON, ILL.
(From the Evanston Hospital)

THE obstetrician is called upon from time to time to assume the responsibility of a case of pregnancy when the woman is having her first baby late in her reproductive life. Does he assume an increased risk and, if so, what are the principal factors?

This study was made in a private hospital with a closed staff where the majority of the cases are handled by a small group of trained men who do nothing but obstetrics and gynecology. The period of time during which these 288 primiparas, over 35 years of age, were delivered was about sixteen years. The 300 primiparas under the age of 25, used for comparison, were consecutive cases of the same character, but their delivery dates do not correspond to the same years. They were delivered by the same men, however, and during a shorter period of time.

TABLE I. DURATION OF LABOR, INCIDENCE OF LABOR, AND CESAREAN SECTION COMPARED

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Number of cases	300	237	51
Duration of labor:			
Average	12 hr.	14 hr.	18 hr.
Shortest	1 hr.	1 hr.	1 hr.
Longest	72 hr.	52 hr.	73 hr.
Toxemia	2.3%	10.9%	13.7%
Cesarean sections	2.0%	17.3%	29.4%

Table I shows that the average length of labor is increased, but the duration of labor is of little importance. It is quite important, however, to note that toxemia increases with age. Admitting that the cause of eclampsia is yet unknown, we must assume that the excretory function decreases in efficiency as one's body grows older. The incidence of cesarean section does not increase because of necessity but probably because of fear both on the part of the doctor as well as the laity. It increases also because more of the risk is put on the mother and less on the baby, in order to assure a living child and what, in many cases, will be that family's only offspring. It increases also because mal-presentations and toxemia increase. It is fairly safe to assume that any group of doctors skilled in the same surgical specialty would also show the same increased incidence of sections. Table IV gives the reasons for cesarean section recorded on the charts.

*Presented at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

CASE 11.—This infant was thought to be at term and was delivered by elective low cervical cesarean section because of a rather small pelvis. Infant weighed only 4 pounds 12½ ounces and lived only 5½ hours. Autopsy showed fluid in respiratory tract and cause of death given as asphyxia neonatorum.

CASE 12.—Full-term infant weighing 8 pounds 7 ounces delivered by breech extraction after a seven-hour labor. Both arms extended above head during extraction. Stillborn infant. Autopsy showed tentorial laceration on right side, subdural hemorrhage and asphyxia neonatorum.

CASE 13.—A full-term infant weighing 6 pounds 11 ounces. Mother had a premature rupture of B.O.W. with loss of most of amniotic fluid. A dry labor of twenty-five hours or more, terminated by manual dilatation of cervix and a high forceps application. Mother's heart decompensated during labor, but recovered. During six hours before delivery patient received 7½ of a grain of morphine. N₂O and ether used. Infant stillborn. Autopsy of infant showed cerebellar damage. Hemorrhages in leptomeninges and beneath scalp.

There were no maternal deaths among the 300 primiparas under 25, and three deaths of mothers 35 and over. All three of the mothers who died were delivered by cesarean section. Case histories are, briefly, as follows:

Mrs. C. H., aged 40, para i. Admitted Jan. 5, 1922. Pre-eclamptic toxemia. Albumin ++. Blood pressure 158/98. Edema. Cesarean section Jan. 6, 1922, and two fibroids removed at time of section. Jan. 7, 1922, marked abdominal distention. Restlessness and by 8:00 P.M. pulse very rapid and patient in shock. Jan. 8, 1922, at 2:00 A.M. patient died. No post mortem. Abdominal incision opened and no abdominal pathology noted. Cause of death given as acute cardiac dilatation.

Mrs. J. B., aged 37, para i. Admitted July 8, 1931, at term. Mitral (rheumatic) disease and pre-eclamptic toxemia. Albumin ++. Blood pressure 158/106. Anesthetic one hour. Ethylene. No complications during cesarean section. Postoperative course marked by emesis and distention on second day. Given gastric lavage repeatedly and intravenous and subcutaneous fluids. On third day postoperative temperature and pulse began to rise and patient died on fifth day. Temperature reached 107° F. terminal. Blood transfusion was being given at time of death. Autopsy showed multiple pulmonary embolism, hemorrhagic infarcts of the right lung (involving 75 per cent of right upper lobe), thrombotic endocarditis of the mitral valve, mitral stenosis.

Mrs. M. H., aged 40, para i. Admitted Apr. 8, 1923. Transverse position. Cesarean section done April 10, 1923. Very smooth postoperative course. Up in chair on April 21. Sudden pain in chest, cyanosis, dyspnea, and death in fifteen minutes. Post mortem refused by husband. Signed out as pulmonary embolism.

Among the 288 patients over the age of 35, there were 19 in whom the presence of fibroids was a complicating factor; whereas, among the 300 young primiparas there were no cases recorded. Among these 19 cases there were 11 cesarean sections. Five of these women had toxemia also, an added reason for section. Four of the other 8 patients were delivered by forceps and 4 were spontaneous. Six of these cases could not be traced, but the other 13 were disposed of as follows:

Myomectomy at time of cesarean section	3 cases
Porro cesarean section	1 case
Subsequent hysterectomy	3 cases
Subsequent myomectomy	1 case
Tumors still present when last seen	3 cases
Spontaneous involution	2 cases

Table VI shows the classifications of fetal deaths called "unavoidable."

TABLE VI. UNAVOIDABLE FETAL DEATHS

	AGE UNDER 25	AGE 35-39 YR.	AGE 40 AND OVER
Under 7 months	2	1	2
Dead before labor	3	2	
Monsters	2		1
Abruptio placentae at 8 months. F.H.T. lost in first stage.		1	

The 13 cases of fetal death, classed as obstetric, were as follows:

CASE 1.—Full-term infant weighing 7 pounds 5 ounces delivered after a labor of eleven hours. N_2O and ethylene used. Occiput posterior with manual rotation and forceps. Fetal heart tones very slow and could not be resuscitated. Autopsy report asphyxia neonatorum.

CASE 2.—Full-term infant whose weight was not recorded. Delivered spontaneously after seven hours of labor. Pantopon gr. $\frac{1}{6}$ and scopolamine gr. $\frac{1}{300}$, given $1\frac{3}{4}$ hours before delivery. N_2O used. Required resuscitation and did very poorly, dying $13\frac{1}{2}$ hours after birth. No autopsy.

CASE 3.—Full-term infant, weighing 8 pounds 3 ounces delivered by low forceps and episiotomy after five hours of labor. Pentobarbital gr. $7\frac{1}{2}$, scopolamine gr. $\frac{1}{150}$, given four hours before delivery. N_2O and ethylene. Infant cyanotic at birth and never did well. Died on third day in a cyanotic attack. Autopsy showed partial pulmonary atelectasis.

CASE 4.—A full-term infant weighing 8 pounds 14 ounces, presenting by breech. Labor lasted $12\frac{1}{2}$ hours. Given morphine gr. $\frac{1}{4}$ and atropine gr. $\frac{1}{150}$, one and one-half hours before delivery. N_2O and drop ether used. Breech extraction was done and the head became arrested in the midpelvis. Forceps were applied and a dead baby delivered. Autopsy showed asphyxia neonatorum.

CASE 5.—A 4 pound-14 ounce baby, born four weeks, prematurely after a nine-hour labor. Delivered by low forceps and episiotomy. Infant died in twenty-four hours. Autopsy showed prematurity, bilateral laceration of tentorium, intracranial hemorrhage and pulmonary atelectasis.

CASE 6.—A full-term infant delivered by low forceps after a rather difficult labor of thirty-one hours. Infant did poorly and died fifteen hours later. Autopsy showed a hemorrhagic pneumonia.

CASE 7.—This infant was four weeks premature and weighed 6 pounds 5 ounces. Given pantopon gr. $\frac{1}{8}$ and scopolamine gr. $\frac{1}{150}$, three hours before delivery. N_2O and ether used. Spontaneous delivery after a fifteen-hour labor. Died $3\frac{1}{2}$ hours later. No autopsy.

CASE 8.—A full-term infant weighing 7 pounds 8 ounces delivered after a labor of twelve hours. Given pantopon gr. $\frac{1}{8}$ and scopolamine gr. $\frac{1}{300}$, four hours before delivery. N_2O and ether used. With head above the spines, B.O.W. ruptured artificially and the cord prolapsed. Forceps applied and a stillborn infant delivered.

CASE 9.—This infant was four weeks premature. The duration of labor was not stated. Infant weighed 4 pounds 1 ounce, delivered spontaneously and lived but seven hours. Autopsy findings were prematurity, cerebral hemorrhage and pulmonary atelectasis.

CASE 10.—A full-term infant according to due date. Delivered after an eighteen-hour labor by low forceps and episiotomy after about three hours in second stage. N_2O and ethylene used. Fetal heart tones were lost after forceps were applied. Infant was stillborn and not weighed. No autopsy.

PELVIC MEASUREMENTS OF 4,144 IOWA WOMEN*

WILLIAM F. MENGERT, M.D., IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology, State University of Iowa)

THERE are so few reports from the United States of large series of pelvic measurements it is felt another is warranted. This seems especially true with regard to the present series which was obtained from women who represent predominantly a rural population. According to the 1930 official census 60.4 per cent of the inhabitants of Iowa live in communities of less than 2,500 population, and 39.6 per cent actually live on farms.

Therefore the purposes of this report are: (1) to present the average pelvic measurements of Iowa women, (2) to discuss the incidence of contracted pelvis in Iowa, and (3) to note the effect of pelvic contractions managed conservatively on labor, mother and child.

SUBJECTS

Between July 1, 1926, and Aug. 1, 1936, 6,426 women were delivered on the Obstetric Service at the University Hospitals. The overwhelming majority of these women have had ample opportunity to be exposed to sunlight, but their dietary is probably inadequate in certain particulars and should be described. The carbohydrate intake of the average Iowan is excessive, due to the consumption of large quantities of potatoes and bread. The protein content of the diet, although apparently adequate, is derived largely from pork with a fat content above average. Although milk and dairy products are produced in quantity, the per capita consumption falls below that of such dairy states as Minnesota, Wisconsin, Illinois, and New York. During the spring and early summer small fruits and vegetables are eaten in average quantity, but during the late summer and winter the consumption becomes progressively more inadequate.

The women of the present series represent a group which is overwhelmingly white, largely American born, but of mixed ancestry. The percentage of negroes in the population and in the present series is so small that it has been disregarded in the statistical analyses.

Among the 6,426 women, the pelvic measurements of 4,144 were considered to be sufficiently accurate to be available for the purposes of the study.

Of the total group of 6,426 women, 234 or 3.65 per cent had some type of contracted pelvis. Although seven of this group died undelivered or were delivered elsewhere, the measurements are included.

*Presented at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

A word of caution should be spoken about myomectomy at the time of cesarean section. Subsequent myomectomy is safer, due to the profuse hemorrhage that generally occurs when one attempts to remove fibroids at the time of cesarean section. The fibroid generally undergoes marked involution at the same time as the uterus.

Only 25 of the 51 patients, delivering for the first time at the age of 40 or over, could be traced. Twenty of these stated that both mother and offspring were well. One mother said that her baby, now 13 years of age, had been an invalid since birth by cesarean section; the nature of the invalidism was not given. One mother refused to give any particulars about her welfare or that of her baby. Three patients had developed cancer and two of these had already died. The third patient was recently operated upon for cancer of the rectum.

CONCLUSION

1. When one assumes the responsibility for an obstetric patient who has her first baby in the later years of her reproductive life, one assumes more responsibility than if the patient were at the age of 25 or under.

2. The incidence of toxemia, prematurity, post-partum hemorrhage, malpresentation and myomas in primiparas, increases with the age of the individual.

636 CHURCH STREET

DISCUSSION

DR. RUDOLPH W. HOLMES, CHICAGO.—For many years I have taught students that they will have the same ease or difficulty, whether an obstetrical patient be 15 or 45 years of age. In other words, the bony structure, from an obstetric viewpoint, is fixed by the time the young woman enters the childbearing period except for the remote possibility of the development of osseous pelvic tumors or of true osteomalacia. Likewise, the soft parts retain their texture during the entire reproductive period except for rare instances of lesions appearing in later life. My conviction has been, therefore, that mere age has a very trivial influence on the type of labor. This belief is contrary to common teaching, but there have been numerous treatises, covering large series of case reports to substantiate my position. It is true, of course, that women who reproduce after 35 will have a somewhat higher incidence of cardiac, nephritic, and hepatic diseases, which complicate the conduct of their labors, but will not affect the type of labor.

It is, of course, true that an elderly primipara may require special management to safeguard her possible last chance of reproduction, a type of management which would be unjustifiable, yes unscientific in a much younger woman.

sonably be expected, it is common practice to attempt measurement of the various pelvic diameters in quarter, or even smaller fractions of a centimeter. Such refinements in technic do not represent greater accuracy, as they are generally subjective estimates rather than objective measurements. This point is demonstrated admirably when measurements are plotted in a frequency bar diagram, and is illustrated in Charts 1 and 2 in the case of the bisischial diameter. Chart 1 shows the class fre-

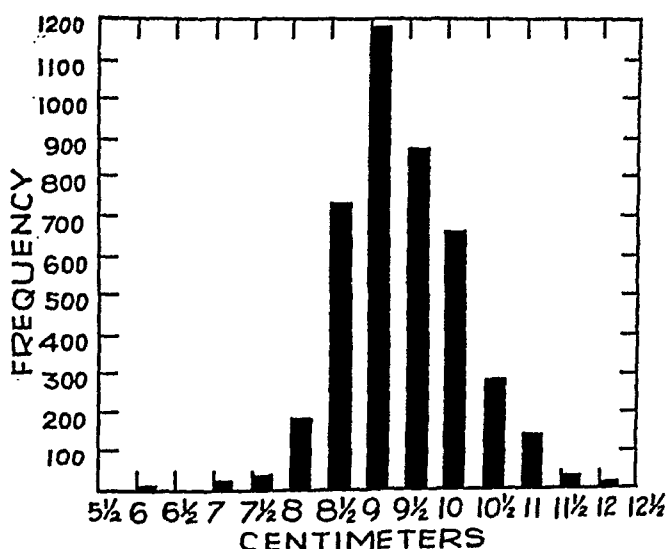


Chart 1.—Showing a frequency diagram of 4,144 bisischial measurements plotted in quarter-centimeter divisions. Note that there is a distinct negative bias.

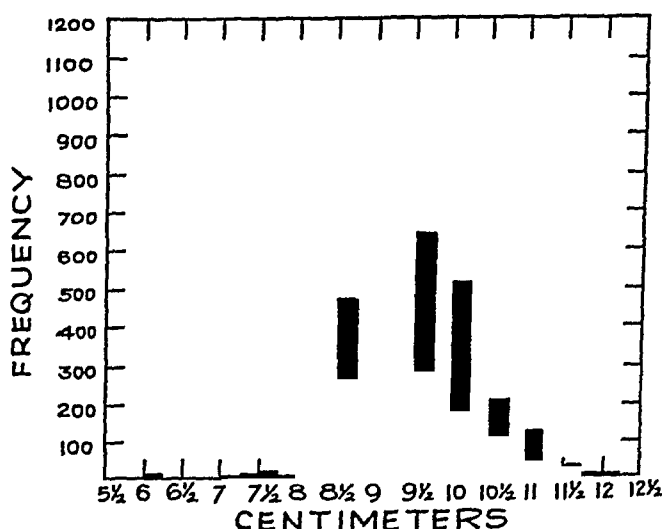


Chart 2.—The quarter-centimeter divisions of Chart 1 have been eliminated by adding half of the frequency of each to the next higher, and half to the next lower class. Note that the frequency distribution is more nearly normal, suggesting that recording of pelvic measurements in less than half-centimeter divisions represents subjective estimation.

quency when plotted as measured. It will be seen that there is a distinct negative bias in the quarter and three-quarter divisions. Chart 2 shows the same data regrouped into half-centimeter divisions. The frequency in each quarter and three-quarter division was divided by two, and half of each of these frequencies allotted to the next higher and half to the next lower division. It is apparent that by so doing, the frequency distribution is more nearly normal. Consequently, it is sug-

METHODS

Accurate mensuration of the pelvis in the living subject requires considerable practice. Therefore, for the purposes of this study, measurements made by a member of the department staff lower in rank than resident were not considered sufficiently accurate and were excluded. The obstetric resident in each instance had served at least three hospital years (two in obstetrics) and had had reasonable opportunity to develop the technic of pelvic mensuration.

Seven pelvic measurements are commonly made: the interspinous, intercrystal, external conjugate or Baudelocque's diameter, bisischial or transverse diameter of the outlet, anterior sagittal, posterior sagittal, and anteroposterior. The intertrochanteric measurement is not done routinely. Determinations of 4,144 of each of the seven common pelvic measurements were available for statistical analysis.

In addition, the diagonal conjugate is measured routinely when the patient is admitted prior to the tenth lunar month of pregnancy, or if there is indication of contracted inlet such as non-engagement of head in a primigravida, or obvious disproportion. However, the majority of this group were admitted within the last month of pregnancy so that, in the absence of indication of contracted inlet, measurement of the diagonal conjugate was not done. Therefore, only 972 attempts were made to measure the diagonal conjugate, and of these the sacral promontory was beyond reach of the examining finger in 865 patients.

In addition, individual study of each contracted pelvis was made in order to ascertain the incidence of the various types, the effect on the clinical course of labor, and on the mother and child.

RESULTS

1. *Average Pelvic Measurements of Iowa Women.*—The average pelvic measurements, the range, and probable errors are recorded in Table I, and with the exception of the bisischial agree closely with common teaching. However, a textbook of obstetrics¹ in general use states, "The transverse (bisischial) diameter measures 11 cm." In the present series of 4,144 women the chances statistically are twenty-one to one that the true mean of the series lies between 7.77 and 10.84. Therefore, there seems to be very little justification for assuming 11 cm. to represent the true measurement of the transverse (bisischial) diameter of the pelvic outlet of Iowa women.

With the bisischial measurements, tests for normality of the series showed that B_1 equals 0.101 and B_2 , 3.067. The value of B_2 falls well within the 5 per cent limits of the Pearson² criterion for normality, while the value of B_1 falls outside the 1 per cent limit. Therefore, the chances are reasonable that the observations are normally distributed.

TABLE I. AVERAGE PELVIC MEASUREMENTS OF 4,144 IOWA WOMEN
(CENTIMETERS)

Note that with the exception of the bisischial measurement, these results agree closely with common teaching.

	AVERAGE	PROBABLE ERROR	RANGE
Interspinous	25.5	1.09	21.0-31.5
Intercrystal	28.0	1.14	19.5-34.0
External conjugate	19.6	0.85	15.0-25.0
Bisischial	9.3	0.51	6.0-12.0
Anterior sagittal	6.2	0.43	4.0- 9.5
Posterior sagittal	7.8	0.38	5.5-10.0
Anteroposterior	11.4	0.43	8.0-13.5

Although it has generally been conceded that agreement within a half centimeter between any two staff members represents as high a degree of accuracy as may rea-

TABLE III. INCIDENCE OF CONTRACTED PELVIS

Note that pelvic contraction occurs nearly four times as frequently in the Hopkins as in the Iowa clinic. Although accurate measurements were available for only 4,144 women; the total number (6,426) of women delivered during the given period of time was used to calculate incidences of contracted pelvises as it was felt that 234 represents *all* of the contracted pelvises observed during this time.

	JOHNS HOPKINS* 6,407 WHITE WOMEN			IOWA 6,426 WOMEN		
	NUMBER OF PATIENTS	IN- CIDENCE	PER CENT OF CON- TRACTED PELVIS	NUMBER OF PATIENTS	IN- CIDENCE	PER CENT OF CON- TRACTED PELVIS
Generally contracted, in- cluding generally con- tracted funnel	345	538	39.98	41	0.64	17.5
Funnel, typical	289	5.03	33.49	156	2.43	66.7
Simple flat	156	2.43	18.07	25	0.39	10.7
Generally contracted rachitic	33	0.52	3.82	1	0.02	0.4
All others	40	0.63	4.63	11	0.17	4.7
Totals	863	13.99	99.99	234	3.65	100.0

*From Stander, H. J., *Williams Obstetrics*.

such exposure is significant is debatable. Another possible explanation of the difference in incidence involves the element of time, for, with rickets less common than formerly, statistics collected forty or more years ago may show a greater incidence of pelvic contractions on a rachitic basis.

Although typical funnel pelvis is generally thought to be a developmental phenomenon and to have similar incidences among all reported races, 5 to 6 per cent, the incidence among the present series is 2.44 per cent, less than half that reported by other observers. Even when all types of funnel pelvises are included the incidence is only 2.55 per cent. It is conceivable that the method of measuring the bisischial diameter differs slightly from that used elsewhere, and that this may account for the low incidence of funnel pelvises. With this in mind, the number (186) of pelvises with bisischial diameters of 8.25 cm. was added to those (156) previously classified as funnel. The resulting total (342) gives an incidence of 5.33 per cent, a figure which agrees closely with that generally given. On the other hand, by adoption of the statistical method previously used, namely dividing the frequency (186) of the 8.25 cm. division by two and allotting one-half (93) to the 8.0 cm. meter class and the remainder to the 8.5 cm. class, the total number of funnel pelvises becomes 249, an incidence of 3.87 per cent, which is still below that generally given. No explanation is offered for the low incidence of this type of pelvic contraction among the group of Iowa women.

3. *Effect on the Clinical Course of Labor.*—Among the various types of contracted pelvises, the incidence of operative interference, Table IV, ranges from 26.9 to 54.5 per cent. However, when low forceps operations and breech extractions are excluded, the range is from 20.0 to 36.4 per cent. Obviously, low forceps operations and breech extractions were not done because of the pelvic contraction, except in funnel pelvises, where low forceps was employed to overcome outlet dystocia, and in one instance where version and extraction of the aftercoming head was necessary.

The average lengths of the first and second stages of labor were calculated for individuals representing each type of pelvic contraction, but no significant variations from normal were observed.

4. *Effect on the Mother.*—There were four maternal deaths among the group of contracted pelvises, Table V, a gross maternal mortality rate of 1.7 per cent. One of these women was admitted at term in extremis from a four-year-old bilateral carcinoma of the breasts with extensive metastases. Her death, four days after low forceps operation done to shorten the second stage of labor, can hardly be associ-

gested that even an observer with years of experience in pelvic mensuration is beyond the limits of reasonable accuracy when recording measurements in fractions smaller than a half centimeter.

Because of the small number (972) of attempts to measure the diagonal conjugate and because in 865 of these attempts the sacral promontory was not reached, the figures for the diagonal conjugate were not submitted to statistical analysis, but are recorded in Table II.

TABLE II. DIAGONAL CONJUGATE*

Note that although 972 attempts to measure the diagonal conjugate were made, only 71 measured $11\frac{1}{2}$ cm. or less.

DIAGONAL CONJUGATE MEASURED LENGTH CM.	NUMBER OF PATIENTS	DIAGONAL CONJUGATE MEASURED LENGTH CM.	NUMBER OF PATIENTS
$6\frac{1}{2}$	1	11	17
8	1	$11\frac{1}{4}$	8
$8\frac{1}{2}$	1	$11\frac{1}{2}$	13
9	1	$11\frac{3}{4}$	3
$9\frac{3}{4}$	2	12	14
10	6	$12\frac{1}{4}$	5
$10\frac{1}{4}$	4	$12\frac{1}{2}$	13
$10\frac{1}{2}$	13	$12\frac{3}{4}$	1
$10\frac{3}{4}$	4	Total	107

*In 865 additional patients, the diagonal conjugate could not be reached.

2. *Incidence of Contracted Pelvis.*—Any patient whose routine measurements suggested contracted pelvis, or who experienced unusual difficulty during labor, was rechecked. In all, 234 patients (3.65 per cent) with contracted pelvises were noted among the total group of 6,426 women. This figure, the total number of women delivered during the given time period, was used to calculate the incidence of pelvic contraction rather than 4,144, the figure on which the statistical calculations of the normal pelvic measurements are based. The reasons for using the figure 6,426 in calculating the incidence of contracted pelvis are: (1) it represents the *total* number of women delivered during the given period of time, (2) it is felt that the rechecking of pelvic measurements following difficult labor gives reasonable assurance that 234 represents the *total* number of women with contracted pelvises observed during the same period. The criteria adopted for inlet contraction were those advanced by Litzmann,³ viz.; the true conjugate measures 9.5 cm. or less in flat, and 10.0 cm. or less in generally contracted pelvises. Williams⁴ advanced the criterion adopted for outlet contraction, viz.; a bisischial (transverse) diameter of 8.0 cm. or less.

Table III shows the total incidence of pelvic contraction as well as the relative incidence of each type, contrasted with the figures for white women given by Williams.¹ Although the total number of women in each series is nearly identical, pelvic contraction was noted nearly four times as frequently in the Hopkins as in the Iowa clinic. Reynolds⁵ reporting on 2,227 Boston women gives an incidence of contracted pelvises among patients requiring obstetric operations of 1.7 per cent, but had he included all of his patients, the incidence would have been 6.8 per cent. Flint⁶ reported an incidence of 8.46 per cent among 10,233 women in New York City. In both Reynold's and Flint's papers funnel pelvises are not included, as their reports antedate by nineteen and twelve years, respectively, Williams'⁴ contribution on contractions of the pelvic outlet. Revision to include the usually accepted figures for incidence of funnel pelvis would raise Reynold's estimate to 11 or 12 and Flint's to 14 or 15 per cent.

The explanation for the low incidence of pelvic contraction among the women of the present series is obscure. Adequate formation of pelvis of Iowa women is presumably not due to dietary measures, as the average diet tends to be deficient in minerals and vitamins. Iowa children, however, apparently have ample opportunity, because the population is essentially rural, to be in the sunlight. Whether or not

cluded. Four term babies died at birth or a few hours thereafter from intracranial hemorrhage. Therefore, these 4 and the 2,248 gm. premature on whom autopsy was not allowed, a total of 5, are the only fetal deaths directly attributable to the pelvic contraction. This represents a fetal mortality rate of 2.1 per cent possibly due to contracted pelvis.

The average weight of the newborn children showed no significant variation from normal.

SUMMARY AND CONCLUSIONS

1. The average pelvic measurements of a group of 4,144 living Iowa women were found to be: interspinous, 25.5 cm.; intercrystal, 28.0 cm.; external conjugate (Baudelocque), 19.6 cm.; bisischial (transverse diameter of the outlet), 9.3 cm.; anterior sagittal, 6.2 cm.; posterior sagittal, 7.8 cm.; anteroposterior, 11.4 cm. With the exception of the bisischial, these measurements agree with common teaching.

2. The fallacy of attempting to measure pelvis more closely than by half-centimeter divisions is pointed out, using the bisischial measurement as an illustration.

3. Among 6,426 women, delivered between July 1, 1926, and Aug. 1, 1936, there were 234 contracted pelvises, an incidence of 3.65 per cent.

4. Typical funnel pelvis was the most common type, accounting for 156, or 66.7 per cent, of the 234 contracted pelvises, or 2.43 per cent of the total series of patients. Generally contracted, including generally contracted funnel pelvises, numbered 41, 17.5 per cent of the contracted group, or 0.64 per cent of the total series. Simple flat pelvises numbered 25, 10.7 per cent of the contracted pelvis group, while the remaining 12 contracted pelvises were of miscellaneous classification.

5. The uncorrected incidence of operative interference was 29.1 per cent. By excluding operations not directly indicated by the contracted pelvis, the corrected operative incidence was 23.1 per cent.

6. Two mothers perished from operations done because of the pelvic contraction, a mortality incidence of 0.85 per cent.

7. Five fetal deaths, a mortality rate of 2.1 per cent, were directly attributable to the pelvic contraction.

The author wishes to express his appreciation to Miss Maxine Ball for her assistance in collecting the data for this paper.

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DISCUSSION

DR. CALVIN R. HANNAH, DALLAS, TEX.—In my opinion the important point in this excellent paper is that the frequency of contracted pelvises is probably about 3.5 or less than 4 per cent. Another excellent point he has brought out is the measurement of the outlet.

ated with the funnel pelvis. Another woman died undelivered at term from a proved gas bacillus (*B. Welchii*) infection. The other two deaths were sequels of operations done because of the pelvic contractions. The corrected maternal mortality rate becomes, therefore, 0.85 per cent.

TABLE IV. OPERATIVE LABORS

Showing the number and percentage incidence of operations, presumably necessitated by the pelvic deformity.

	NUMBER OF PATIENTS	NUMBER							TOTAL OPERATIVE INCIDENCE		
		CESAREAN SECTION		FORCEPS			BREECH		NUMBER	PER CENT	
		CLASSIC	LOW	HIGH	MID	LOW	VERSION AND EXTRACTION	BREECH		UNCORRECTED	CORRECTED
Generally contracted, including generally contracted funnel	41	5	4	-	-	2	-	1	12	29.3	21.9*
Funnel, typical	156	12	-	-	3	20	1	6	42	26.9	23.1†
Simple flat	25	3	1	1	-	3	-	-	8	32.0	20.0*
Generally contracted rachitic	1	-	-	-	-	-	-	-	-	-	-
Miscellaneous	11	3	-	-	1	1	-	1	6	54.5	36.4*
Totals	234	23	5	1	4	26	1	8	68	29.1	23.1

*Low forceps and breech excluded.

†Breech excluded. The version, done because of the contraction, is included.

TABLE V. MATERNAL AND FETAL MORTALITY
(ACTUAL NUMBERS)

Showing the total number of maternal and fetal deaths in the series, and the number presumably attributable to the pelvic deformity.

	MATERNAL		FETAL	
	TOTAL	CORRECTED	TOTAL	CORRECTED
Generally contracted, including generally contracted funnel	0	0	3	0
Funnel, typical	2	0	14	5
Simple flat	1	1	0	0
Generally contracted rachitic	0	0	0	0
Miscellaneous	1	1	1	0
Total	4	2	18	5

5. *Effect on the Child*.—There were 18 stillborn and neonatal deaths, a gross fetal mortality rate of 7.8 per cent. However, of these, 4 were abortions (fetuses weighing less than 1,500 gm.), 4 were stillborn macerated fetuses obviously dead before the onset of labor, and 4 were premature infants (1,500-2,500 gm.). Three of the prematures who succumbed after birth were shown at post-mortem examination to have perished from prematurity alone, or from prematurity and atelectasis, and therefore, these deaths cannot be ascribed to the pelvic deformity. However, the fourth, weighing 2,248 gm., died the day after birth and permission for post-mortem examination was withheld. One infant with a prolapsed cord died before birth, as a result of compression of the cord with a Voorhees' bag inserted following replacement of the funis. Another stillbirth resulted from premature separation of the normally implanted placenta. These two deaths presumably may also be ex-

symptomatology of the condition resulting in a greater number of early diagnoses, (2) a more universal appreciation of the dangers resulting from untimely interference, (3) improved operative technic, (4) marked advancements in the field of anesthesia, (5) recourse to blood transfusions, and (6) more adequate maternity facilities in the smaller communities. Fortunately, there is now little necessity for handling these cases in the private home under conditions which, even at best, are inadequate. This one factor alone has to a large extent reduced the incidence of infection, one of the two greatest complications.

I present the collected case reports under two headings: (1) those reported up to and including the year 1921, and (2) those reported from 1922 to the present time. These two groups of cases are sufficiently large, I believe, to give a fairly accurate picture of the types and results of the therapeutic measures in vogue during the respective periods.

It will be noted that no mention is made of the corrected fetal mortality, due to the circumstance that most of the reports failed to refer to this item. Instead, all fetal deaths of whatever period of gestation and under all conditions are grouped together.

There has been no unanimity in the classification of placenta previa. In my review, cases in which the placenta has completely covered the internal cervical os will be spoken of as *complete previas*; those in which the margin of the placenta has partially covered the internal os will be called *marginal previas*; and those in which the edge of the placenta borders on or touches the internal os will be classed as *lateral previas*.

The total number of cases reviewed is 47,828, or more than twice the number ever before collected. The frequency of the condition has been variously stated from 1 in 34 to 1 in 506 pregnancies. In a series of 21,706 cases I found the incidence to be 1 in 159.6 (0.626 per cent). In 9,513 cases 2,830 (29.75 per cent) were of the central type, 3,127 (32.87 per cent) were marginal, 3,525 (37.05 per cent) were laterals, and 31 (0.33 per cent) were of unknown classification.

Abnormal position of the fetus is common and may be considered as one of the suggestive diagnostic features. Cephalic presentations were found in 687 (71.19 per cent) of 965 cases, breech presentations in 130 (13.48 per cent), transverse lies were present in 146 (15.13 per cent), and in 2 (0.2 per cent) the position of the baby was not known.

A great predominance of cases was found in multiparas. In a total of 21,111 cases placenta previa was found to occur in 2,918 primiparas (13.82 per cent) and in 18,193 multiparas (86.18 per cent).

It has often been stated that placenta previa is a complication of the third trimester of pregnancy. This is the rule. However, it is well known that symptoms may arise at any time after the formation of the placenta. It was found to occur in 3,753 (84.98 per cent) of 4,416 cases after the thirty-first week of gestation and in 663 (15.02 per cent) prior to this period.

TABLE I. PLACENTA PREVIA

Cases before 1922:	
Number	15,062
Maternal mortality	1,166 (7.74%)
Gross fetal mortality	7,876 in 14,162 cases (55.61%)
Cases from 1922 to 1937:	
Number	32,766
Maternal mortality	2,288 (6.98%)
Gross fetal mortality	6,551 in 12,885 cases (50.84%)

The physicians throughout Texas are probably no different from those of other states, but as we go about teaching through refresher courses it is astounding that the number of physicians who do not know how to make pelvic measurements is so great. We found in a class of 15 or 20 good physicians that less than three men knew how to make measurements. It is up to us as members of this Society to disseminate this information and to teach the men in the rural districts as well as those in the cities how to use a pelvimeter. They must understand that they cannot estimate the size of the pelvis by palpation but that they must do it by practical work and by measurements.

MANAGEMENT OF PLACENTA PREVIA*

AN ANALYSIS OF 47,828 CASES

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N EARLY three centuries have passed since Paul Portal (1664) demonstrated for the first time that in placenta previa the afterbirth is embedded over the cervical os. Earlier observers, to the time of Hippocrates, recognized the seriousness of the condition but believed the resulting hemorrhages were due to the premature detachment of the placenta located, as they thought, in the fundus. The observations of Portal awakened a lively interest in placenta previa and we find Mauriceau, Pugh, Deventer, Smellie, Levret and a host of other obstetricians of the seventeenth, eighteenth, and nineteenth centuries advocating means of control of the hemorrhages and the speedy delivery of the baby and afterbirth.

While the records of earlier times reveal a marked improvement in results, as expressed in maternal and fetal mortalities, it may be said that it is in quite recent years that the greatest advances have been made. Great as has been this progress the maternal and fetal mortalities are yet far too high. Of this I became more convinced as I undertook an extensive statistical review of the literature. To the cases already recorded I have added 62, previously unreported, from the records of the Philadelphia Lying-in Hospital, covering a period from July 1, 1929, to June 30, 1935. It is hoped that this large series of cases, taken from the records of clinicians and institutions the world over, will throw some light on the treatment of placenta previa and the comparative results of the various methods now in common usage. All available statistics have been carefully studied and an impartial analysis has been made.

As will be shown later, the therapeutic trend has changed markedly in the past ten to fifteen years, with increasingly more satisfactory results for both mother and child. This change may be accounted for in several ways: (1) a better understanding of the pathology and

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cesarean sections. In other words, the simpler the method used the greater is the chance for the survival of both mother and child. No definite causes of maternal mortality were stated, but it is presumed that the majority of the patients died from shock or infection.

TABLE IV. TYPES OF CESAREAN SECTIONS

Classical:		6,168
Maternal mortality	372 (6.03%)	
Gross fetal mortality	687 in 2,794 cases (24.58%)	
Low cervical:		375
Maternal mortality	7 (1.86%)	
Gross fetal mortality	11 in 67 cases (16.41%)	
Porro:		61
Maternal mortality	8 (13.11%)	
Gross fetal mortality	20 in 28 cases (71.42%)	

It is interesting to note that the incidence of cesarean section has more than doubled during the past fifteen years, and in spite of this great increase in number the maternal mortality has been more than halved; it falls well below the group delivered vaginally. The fetal mortality in abdominal cesarean sections was but slightly decreased but remained much lower than in the group delivered through other avenues. In Table IV we find a comparative list of the various types of abdominal cesarean sections. Although the series of low cervical sections is too small to permit of any definite conclusions it would seem, in the hands of skilled operators, to give both mother and child a better chance for life. The danger of a generalized peritoneal infection is greatly lessened by this procedure because there need be no manipulation of the intestines or omentum, and the general peritoneal cavity can be

TABLE V. TYPES OF PLACENTA PREVIA

METHOD	CENTRAL PREVIA			MARGINAL PREVIA		
	CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY	CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY
Spontaneous	17	0 (0.00%)	13 (76.47%)	175	4 (2.28%)	57 (32.57%)
Ruptured membranes	20	1 (5%)	10 (50%)	144	2 (1.39%)	70 (48.61%)
Pack	28	4 (14.28%)	14 (50%)	133	4 (3%)	80 (60.15%)
Bag	26	2 (7.69%)	12 (46.15%)	30	1 (3.33%)	16 (53.33%)
With spontaneous						
With version	7	1 (14.28%)	0 (0%)	6	0 (0%)	5 (83.33%)
With forceps				6	0 (0%)	1 (16.66%)
With breech						
Breech	8	1 (12.49%)	2 (25%)	7	0 (0%)	1 (14.28%)
Forceps	14	3 (21.42%)	12 (85.71%)	31	1 (3.22%)	18 (58.06%)
Braxton Hicks version	425	47 (11.05%)	362 (85.17%)	486	24 (4.95%)	345 (70.98%)
Version	92	14 (15.21%)	58 (70.72%)	76	2 (2.63%)	14 (18.42%)
Willett	15	1 (6.66%)	15 (100%)	143	7 (4.89%)	80 (55.94%)
Leg traction	132	10 (7.57%)	114 (86.36%)	65	0 (0%)	44 (67.69%)
Craniotomy	8	4 (50%)	8 (100%)	2	0 (0%)	2 (100%)
Accouch. forcé	5	1 (20%)	3 (60%)	2	0 (0%)	1 (50%)
Vaginal cesarean	2	1 (50%)	1 (50%)			
Classical cesarean	504	29 (5.75%)	116 (23.01%)	153	6 (3.92%)	21 (13.72%)
Low cervical	24	1 (4.16%)	1 (4.16%)	2	0 (0%)	0 (0%)
Porro	11	1 (9.09%)	3 (27.27%)			
Undelivered	2	2 (100%)	2 (100%)			
Induction						
Unknown	632	91 (14.39%)	97 (15.34%)	1739	66 (3.79%)	140 (8.05%)
Vaginal delivery	23	3 (13.04%)	?	27	1 (3.73%)	0 (0%)
Abdominal delivery	78	3 (3.84%)	12 (15.38%)	38	0 (0%)	4 (10.52%)
Total	2063	220 (10.66%)	806 in 2040 cases (39.51%)	3266	118 (3.62%)	899 (27.52%)

Table I shows the total series of cases divided into the two group periods. It will be observed that in the past fifteen years both the maternal and fetal mortality rates have been definitely reduced. Upon further examination, and subdividing the cases into those delivered vaginally and those delivered by the abdominal route (see Table II), we can readily see that the major drop in the maternal death rate resulted from an increased adoption of cesarean section. Infant mortality decreased somewhat but not in proportion to the maternal rate. We also note that fewer mothers died after delivery from below. As will be pointed out later, this decrease resulted from the abandonment of certain traumatizing operative procedures, such as accouchement forcé and vaginal cesarean sections. These figures differ somewhat from those recently reported by Mackenzie, who found maternal and fetal mortalities of 6.6 per cent and 17 per cent, respectively, in cesarean sections, and 8 per cent and 53.7 per cent in those delivered by the vaginal route.

TABLE II. GROSS FETAL AND MATERNAL MORTALITY

Cases before 1922—4,627:

Cesarean sections	281 (6.07%)
Maternal mortality	34 (12.09%)
Gross fetal mortality	75 (26.69%)
Vaginal deliveries	4,346 (93.93%)
Maternal mortality	343 (7.89%)
Gross fetal mortality	1,685 in 2,864 cases (58.88%)

Cases from 1922 to 1937—31,935:

Cesarean sections	4,885 (15.29%)
Maternal mortality	293 (5.99%)
Gross fetal mortality	458 in 1,873 cases (24.45%)
Vaginal deliveries	27,042 (84.71%)
Maternal mortality	1,735 (6.41%)
Gross fetal mortality	4,869 in 8,477 cases (57.43%)

In Table III we find listed the various types of vaginal deliveries with their respective maternal and fetal mortalities. From this we learn that repeated, prolonged or complicated vaginal manipulations greatly enhance the risk to both mother and child. This is most noticeable in such methods as internal podalic version, accouchement forcé, ligation of the uterine vessels, craniotomy, and vaginal

TABLE III. VAGINAL DELIVERIES WITH MORTALITIES

METHOD	CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY
Spontaneous	3,068	70 (2.28%)	525 in 2,244 cases (23.39%)
Ruptured membrane	2,070	37 (1.78%)	436 in 1,958 cases (22.24%)
Pack	477	32 (6.71%)	239 in 475 cases (50.31%)
Bag	4,464	263 (5.89%)	1,542 in 3,113 cases (49.50%)
With spontaneous	28	1 (3.57%)	8 in 28 cases (28.57%)
With version	340	13 (3.82%)	77 in 214 cases (35.99%)
With forceps	35	2 (6.14%)	4 in 22 cases (13.63%)
With breech	14	2 (14.28%)	10 in 14 cases (71.42%)
Breech	644	35 (5.43%)	381 in 608 cases (62.66%)
Forceps	224	16 (6.55%)	83 in 197 cases (42.13%)
Braxton Hicks version	10,660	686 (6.43%)	5,523 in 8,213 cases (67.24%)
Version	3,210	359 (11.18%)	1,063 in 2,526 cases (42.08%)
Willett	263	12 (4.56%)	143 in 263 cases (54.37%)
Leg traction	500	36 (7.20%)	358 in 500 cases (71.60%)
Craniotomy	29	6 (20.69%)	29 in 29 cases (100.00%)
Accouch. forcé	291	71 (24.39%)	133 in 282 cases (47.16%)
Vaginal cesarean	1,324	95 (7.17%)	288 in 1,025 cases (28.09%)
Undelivered	22	22 (100.00%)	22 in 22 cases (100.00%)
Induction	15	0 (0.00%)	11 in 15 cases (73.33%)
Unknown			
Total	27,678	1,758 (6.35%)	10,877 in 21,748 cases (50.01%)

SUMMARY

1. An analysis of the management and results of 47,828 cases of placenta previa collected from world-wide literature is presented.

2. The total series is divided into two groups: (1) those reported up to and including 1921, and (2) those reported from 1922 to the present time. The latter group shows a small but definite decrease in both maternal and fetal mortalities over the former. This decrease may be accounted for by (1) a better understanding of the pathology and symptomatology of the condition resulting in a greater number of early diagnoses, (2) a more universal appreciation of the dangers resulting from untimely interference, (3) improved operative technic, (4) marked advancements in the field of anesthesia, (5) recourse to blood transfusions, and (6) more adequate maternity facilities.

3. A subdivision of these two main groups into those patients delivered vaginally and those by the abdominal route is made showing the mortality rates of each. The incidence of cesarean section has increased from 6.07 per cent to 15.29 per cent during the past fifteen years while the maternal mortality rate has been more than halved and falls well below the group delivered from below. A slightly lessened maternal death rate was also noted in those patients delivered vaginally. This decrease is chiefly due to the avoidance of such methods as accouchement forcé, Braxton Hicks version, vaginal packs and vaginal cesarean sections. Tables revealing the results of both abdominal and vaginal methods indicate that repeated, prolonged or complicated manipulations greatly enhance the risks to both mother and child.

4. Further tables show the methods used in handling the various types of previas. With but few exceptions, the various procedures show an increase in mortality rates in direct proportion to the degree of the previa.

5. Low cervical cesarean section is the procedure of choice in complete placenta previa and in other types presenting a closed cervix. In marginal or lateral previas with a dilated cervix the method of choice is between artificial rupture of the membranes with forceps or spontaneous delivery of the fetus and internal podalic version.

6. Blood transfusions are invaluable aids in combating acute anemia and shock and in shortening the period of convalescence. Suitable donors for all suspected cases should be available at the time of delivery. Transfusions should be more frequently resorted to.

7. References are made regarding the frequency of placenta previa, the incidence of the various types of previas, parity, the period of gestation and the presentation and lie of the fetus.

8. As these cases were almost wholly taken from reports of leading obstetricians and maternity centers throughout the world the resulting statistics do not give an accurate picture of the results obtained in general practice. It is fair to assume that the mortality rates in general practice would be much higher than in maternity hospital practice.

better protected against "spill" from an infected uterus. In event of frank infection the Porro operation seems to be the procedure of choice. No mention was found in the literature of the use of the Latzko operation in placenta previa.

In Table V we are able to contrast the results of all methods of management in the various types of previas. From them we may learn one important fact, namely, that the risk for mother and child increases in direct proportion to the degree of the previa. With but few exceptions, the various methods show a reduction in death rates in marginal as compared with complete previas and in lateral as against marginal cases.

Although there were no accompanying statistics there have recently appeared in the literature numerous references concerning the use of blood transfusions in the treatment of placenta previa. There is no doubt that frequent recourse to this life-saving procedure has prevented many casualties. In most maternity centers it is now a routine procedure to procure suitable donors for all suspected cases of placenta previa and to be prepared for immediate transfusion should the necessity arise. I am convinced that in the future this procedure will be more often adopted and will save many lives that are now lost by lack of foresight or inability to obtain suitable blood. It not only is the best method we possess for combating shock and acute anemias but is an excellent prophylactic measure against infection and prolonged convalescence. It should be more often resorted to.

WITH TREATMENT AND MORTALITY

LATERAL			UNKNOWN		
CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY	CASES	MATERNAL MORTALITY	GROSS FETAL MORTALITY
347	0 (0%)	83 (23.91%)			
285	7 (2.45%)	105 (36.84%)			
83	2 (2.41%)	36 (43.37%)			
56	1 (1.78%)	10 (17.85%)			
41	2 (4.87%)	2 (4.87%)			
5	1 (20%)	1 (20.0%)			
26	0 (0%)	7 (26.92%)			
55	4 (7.27%)	13 (23.63%)			
186	14 (7.52%)	104 (55.91%)			
78	6 (7.69%)	30 (38.33%)			
86	3 (3.48%)	42 (48.83%)			
81	2 (2.46%)	58 (71.60%)			
4	2 (50%)	4 (100.0%)			
5	2 (40%)	3 (60.0%)			
92	7 (7.60%)	11 (11.93%)	18	1 (5.55%)	0 (0%)
9	0 (0%)	0 (0%)			
2	0 (0%)	2 (100.0%)	1	1 (100.0%)	1 (100.0%)
15	0 (0%)	6 (40%)			
419	34 (8.11%)	182 (43.43%)	14	1 (7.14%)	3 (21.43%)
35	1 (2.85%)	0 (0%)	8	2 (25.0%)	0 (0%)
66	0 (0%)	8 (12.12%)	3	0 (0%)	1 (33.33%)
2096	88 (4.19%)	707 (33.73%)	44	5 (11.46%)	5 (11.46%)

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DISCUSSION

DR. IRVING F. STEIN, CHICAGO.—In a large proportion of our cases at Michael Reese Hospital simple puncture of the membranes has been one procedure which has been most successful. I cannot resist at this point to call attention to the little ring we have developed at Michael Reese Hospital which we facetiously call the "midwife's fingernail." To rupture the membranes, it is only necessary to flex the finger which releases the notched projection. It can be placed on the gloved finger for any vaginal examination, so in case the membranes should need to be ruptured, it is handy and a second introduction of an instrument is not needed.

In complete previa, particularly in a primipara, cesarean section should be done. Dr. Findley has shown a reduction in mortality with the low cervical section. We have never used the Latzko operation. We have had no deaths after low cervical section in primiparas at term or before term.

Bags are not used by us as a means of delivery, but when podalic version is indicated a bag may be introduced as a preparatory measure. We find ourselves using bags less and less, however. After the bag is out spontaneous delivery may occur, or forceps may be used if the head comes into the pelvis, or podalic version may be done.

In our clinic at Michael Reese Hospital we have practically abandoned Braxton Hicks version.

Accouchement forcé which was responsible in the past for the most serious complications, is now recognized as a distinct menace, and I think should be considered as malpractice.

Packing before delivery, I believe, should only be done when the patient is at home, and has to be transported after severe hemorrhage.

Transfusion is the most valuable adjunct to treatment instituted in recent years. In our hands transfusion by the syringe method has been preferable to the citrate method, though we are doing more and more citrate transfusions. However, reactions are more frequent than with the direct method.

DR. RUDOLPH W. HOLMES, CHICAGO.—We cannot determine the true incidence of placenta previa until we have the statistics upon all births with their complications in large communities, better whole countries. Hospital figures are not the indices of the prevalence of previa, for the rate here is necessarily much higher than at large. I have the records of 249 hospitals in which the average rate for placenta previa was 0.67 per cent. One small hospital had 9 per cent of their deliveries with this complication, and from this point the rates decreased until in one hospital there was but one previa in 2,174 deliveries. The maternal death rate in this series was 9.07 per cent, the fetal death rate 38.57 per cent.

DR. WALTER W. WELLS, OKLAHOMA CITY, OKLA.—In the state of Oklahoma during the year 1936, there were 49,973 deliveries and 159 deaths, 28 of which were from uterine hemorrhage and 7 of these were placenta previa. At the University Hospital for the period from 1927 to 1937 there were 3,764 deliveries with 44 cases of placenta previa. Eight of these cases of placenta previa were placenta previa centralis. There were 22 bag inductions, seven of which were followed by version. Two patients were delivered by cesarean section. There were 17 fetal deaths

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that the patient had a congenital absence of the uterus, associated with congenital abnormalities of the generative tract, bilateral inguinal hernia and mitral heart disease.

She was operated upon June 7, 1935, for bilateral hernia. Both canals were opened, and the masses in both sacs which were adherent to the sac walls were removed. One-half of the uterus was found in each sac along with part of the round ligament, the ovary and the blood vessels. The masses were removed by ligation, the sacs ligated also and the operative route closed by the Bassini method. Associated with the bilateral inguinal hernia, the operation showed that there was present also a congenital prolapse of the ovaries, rudimentary tube, and bisected uterus. The operation, in addition to the bilateral herniotomy, included a bilateral salpingo-oophorohysterectomy.

Gross Anatomy.—The two masses, one removed from the right, the other from the left, groin, presented a smooth peritoneal surface that faced the pelvic cavity and a rough adventitious coat that was embedded in the canal. Over the top of each mass there ran a portion of the round ligament and the degenerated oviduct which ended in a well-developed fimbria but in which no lumen could be sounded with a probe. The small gonads were hard and firm beneath which the broad ligament could be recognized. The uterine portion, one-half of which was associated with each gonad, was hard and infantile in appearance. Roughly each mass was a mirror image of the other indicating that the bilateral components had failed to meet in the median line, and hence, from some unknown period in embryonic development, the bilateral parts of the Müllerian system had pursued independent lines of development and produced bilateral halves of the uterus that eventually descended into the pelvic wall. Inasmuch as the vagina ended blindly, but was otherwise normal in structure, it must be inferred that it and the uterus arose from different and unconnected anlagen, which normally unite and break down to form the functional reproductive system of the female and this observation necessitates a modification of the view that the Müllerian system of the embryo gives rise to the female genitalia as far caudad as the hymen.

The uterine portion of the specimen was composed of a fundus and a body which descended into the pelvic wall where its identity was lost without giving rise to a recognizable cervix. The uterine portion, when examined histologically, was found to be composed of heavy connective tissue strands in abundance which were commingled with sparse and widely scattered smooth muscle strands, so jumbled in arrangement that definite configurations could not be determined. The epithelium was reduced to irregular and intermittent portions of tubules, associated with which were mere suggestions of glands, but in no place could glandular material be seen to suggest any glandular activity nor was the arrangement indicative that a continuous cavity ever existed in the center of the disordered uterus.

The elongated rod which ran over the gonad from the fundus of the uterus forward ended in a membranous fimbria but without an ostium. Sections of the tube revealed an intermittent epithelial lining around short cavities, suggesting that an attempt had been made to form a continuous lumen, but nothing suggested that any such continuous lumen had ever been achieved. Scattered smooth muscle cells were found in the walls haphazardly associated with exaggeratedly developed connective tissue strands that rendered the tube hard and firm. The round ligament was short and difficult to recognize, but the broad ligament was normal in structure, small and attached along the side of each bisected half of the uterus.

Gonads.—The difference in size of the right and left gonads was slight. The right one measured, including the tough fibrous capsule, tunica albuginea, 28.2 by 18.9 by 15 mm. and the left 27 by 13 by 12 mm. The capsule was 2 mm. thick, so that the measurements of the actual gonadal tissue were 24.2 by 14.9 by 11 mm., right and 23 by 9 by 8 mm. left.

Upon section of each gonad the cut surface revealed the presence of coarse and fine granulations among which were small white spherules that could be picked up and teased out with needles whereupon they would break off and float away in the dissecting fluid. Some of them were elongated and so twisted that they resembled the contorted tubules of the testis. Interlaced about the tubules were fine white

and one maternal death. At St. Anthony's Hospital during the same period there were 8,653 deliveries. There were 53 placenta previas, including 10 central placenta previas. Eleven patients were delivered by cesarean section. There were 1 quinine-castor oil induction, 3 versions, and 2 low forceps, 2 of which were followed by transfusion. There were 5 fetal deaths compared with 17 in the University Hospital, and 1 maternal death. The total number of placenta previas reviewed were 97.

Low cervical cesarean section is the operation of choice. In a primipara with undilated cervix and marginal placenta previa, cesarean section should be done. We make it a rule at the University Hospital that no patients with placenta previa leave the hospital undelivered.

AN ANALYSIS OF A HUMAN OVOTESTIS

ASSOCIATED WITH A CONGENITALLY BISECTED UTERUS HERNIATED INTO THE INGUINAL CANALS*

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INTRODUCTION

THE combination of unusual features associated with the malformations constituting the basis of this study are of such unusual excellence that no report of similar conditions has been found in the literature. Ovotestis is not rare and the fact that it is often associated with true or spurious hermaphroditism is likewise well known. Various shades or degrees of anomalies have been classed under the heading hermaphroditism, sometimes loosely and sometimes with careful and detailed analyses. The term "ovotestis" is used here to express specifically a gonad in which are commingled the biologic elements of both ovary and testis in varying proportions which may be either congenitally acquired or the result of faulty development embryologically.

CASE REPORT

The anatomic material furnishing the basis of this study was obtained from a white woman aged 39, who complained that she had never menstruated and at times suffered from severe tenderness in both inguinal regions since the age of 14. Her weight in the past seven years had increased from 98 to 134. The first of her 2 brothers had three children and the second the same number. Four of her 8 sisters are now living, the first of which has 4, and the second 7 children. The third sister has no children but seems to have enjoyed a normal sexual experience while the fourth sister had the same external defects as the patient. Of the dead sisters one died at the age of 49 after having had 10 children, the second died at the age of 16 from the effects of asthma, the third and fourth in infancy.

The physical examination revealed the external appearance of a female normal in stature, voice, and hair line. The normal and feminine appearing breasts became congested at irregular intervals. The abdomen was moderately obese. Bilateral masses, the size of an almond, rested in each inguinal region that were quite tender to the touch.

The vagina was shallow but no cervix could be felt or detected and nothing could be palpated in the pelvis. As a result of the physical examination, it was determined

*Read at the Ninth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Dallas, Texas, October 14 to 16, 1937.

The interstitial material was scanty and no vacuoles or inclusions of any kind could be discerned in the cytoplasm of such cells. The appearance of the tubules, even those measuring 55 micra in diameter, was characteristically embryonic and rudimentary and showed a stage of differentiation attained by the normal testicle at the sixth month of gestation. In no cell was there ever seen any indication of mitotic activity, so that growth in size of the testicular portion was impossible.

Ovarian Material: The ovarian part of the gonad, about three times more extensive than the testicular and much more diffuse, contained a number of degenerating follicles in various stages of disintegration. In none could a true ovum be found, even in the smaller and more primitive follicles that departed least from the normal. The granulosa cells were thinly arranged about the periphery of the follicle, some of them lying loosely in the spaces ordinarily occupied by the liquor folliculi. Small clusters of cells were often met with in the central portions of the follicles leading one to think of them as fragmented ova in advanced stages of dissolution. Often a slight layer of ellipsoidal nuclei surrounded the follicles, the only recognizable remains of the theca interna (Fig. 2).



Fig. 2.

Fig. 2.—Ovarian mass of the ovotestis. $\times 260$.

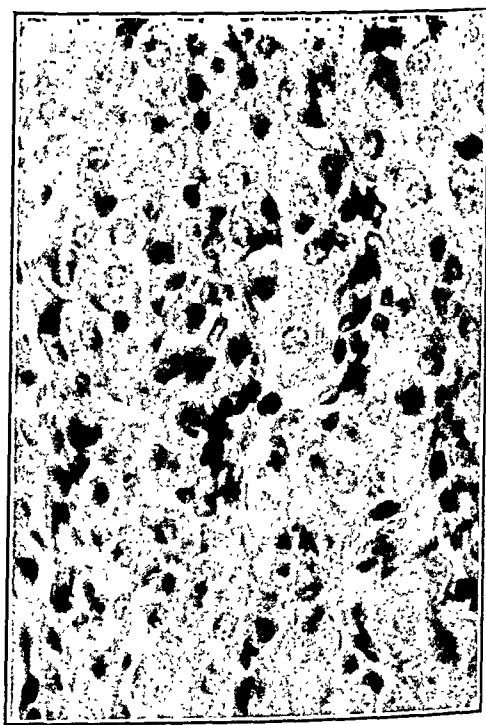


Fig. 3.

Fig. 3.—Ovarian portion of the ovotestis showing the genitaloid cells. $\times 736$.

Associated with the degenerate follicles and lying in the same tissue with them are to be found the areas of diffuse ovarian stroma whose cells, for the most part, are large spherical elements closely recalling the genatoloid cells of the early fetal gonad. These large cells are somewhat vesicular (Fig. 3); the contained cytoplasm, without definite delimiting membranes, contains no conspicuous granules, no vacuoles, and unite diffusely with neighboring cells like them. The ovarian tissue, like the testicular, has attained the differentiation characteristic of a normal fetal ovary of the sixth month.

In neither the testicular nor the ovarian portions were the interstitial cells developed to an excess nor had the cells achieved the structure so characteristic of the specimens described by Jordan and Whitehead. Cells described by them as occurring in their specimens were not found in this one at all. In any case the importance of the interstitial cell as a source of the sex hormone can easily be over-

fibers that seemed to hold them in place. Nothing about the gross appearance of the gonad suggested its sex. Fibrous tissue penetrated into the stroma of the gonad after the manner of trabeculae and definitely delimited areas of different consistency. The areas of varying consistency were equally distributed throughout the gland, but the spherules and contorted tubular structures occupied much less space.

In thick sections (60 micra) under low power magnification (30 diameters), the contrasting areas offered different reactions to the stain. Some portions stained very darkly and others stained very lightly. The darkly staining areas were irregular in outline, and constituted a definite cortex that encroached with varying depths upon the medulla, which in general took the lighter stain. The lightly staining medulla radiated outward to end against the thick tunica albuginea and often to branch two or three times while doing so. Interlaced through the lighter streaks were strands of connective tissue fibers. The fibers were coarse and straight, the cells small, ellipsoidal and often indefinitely outlined. In various places, nodular masses of 2 to 3 mm. in diameter were encapsulated by the connective tissue fibers, which upon closer examination proved to be testicular in nature, while the diffuse, darkly stain-

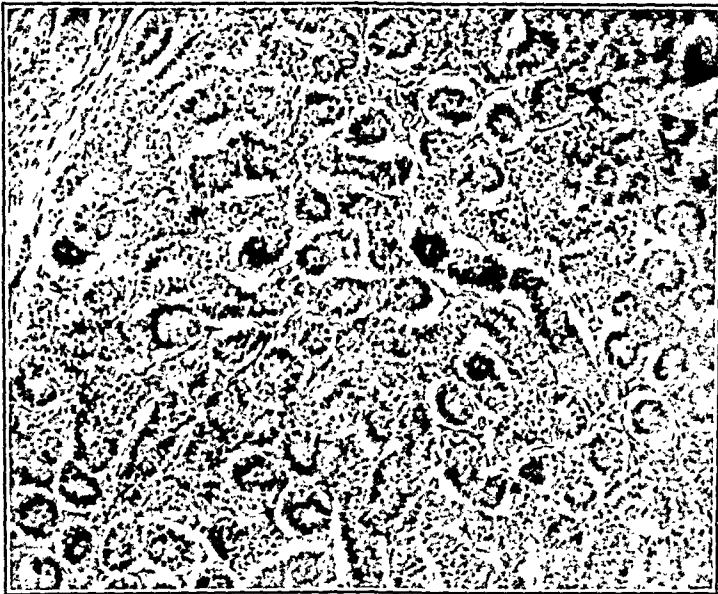


Fig. 1.—Testicular stroma of the ovotestis showing the tubules. $\times 260$.

ing cells, not so definitely encapsulated proved to be ovarian masses. The darkly staining gonogenic tissue showed regional differentiation toward ovarian and testicular materials in the ratio of 3 (ovarian) to 1 (testicular).

Testicular Material: The areas in which testicular material predominated were small and confined to the medullary portion of the cortical zone. The diameter of these spherules and tubules varied from 15 micra to 50 micra. For the most part all sizes were definitely delimited and surrounded by well-formed connective tissue capsules. In the smaller ones the connective tissue was quite thin but in the larger tubules it constituted a definite envelope (Fig. 1). Each testicular area was made up of these tubules which were short, contorted and possessed a definite basement membrane, not always seen clearly in connection with the small tubules, 20 micra or less. Supporting the larger tubules, 50 micra, the basement membrane was clearly visible on account of the inner cells having shrunk away from its inner surface. The cells within the larger tubules which may be likened to the spermatogonia were never more than two layers thick, often they were vesicular, and placed around a central space free from cells not unlike the lumen of a normal, embryonic tubule. It is in this space, or lumen where spermatids form and metamorphose into spermatozoa, but no cells approaching spermatogonia of the second order could be found, nor were there any indications anywhere that spermatids had ever been proliferated.

On the other hand, however, the male hormone is necessary for male somatic differentiation. Even in the presence of the female hormone the male hormone forces the individual organism toward maleness, because the female hormone is superseded by the male. The immature gonads if stimulated by both male and female hormones progress toward male somatic differentiation and the ovarian tissue of the gonad is gradually replaced by testicular tissue.

The results of extensive experiments by Wiesner have prompted him to discard the dihormonic theory of sex causation and accept a monohormonic basis. His work, supported by that of Moore and Price, goes on to show that estrin, even if antiorchidic, is not a direct feminizer, and hence, is not concerned with female differentiation somatically. The male sex hormone is not so much antagonistic to female differentiation, but rather that it supersedes the inherent tendency of the organism towards female differentiation and forces it out and on beyond the female limits into the category of the male.

The testis hormone has no effect upon spayed females, but it does prevent the appearance of castration effects in males. Estrin does not hasten the involution of male sex characters when given to castrates, but when given in excessive amounts to normal males damages the testes and accessory organs. If both estrin and the male sex hormone are given at the same time the damaging effects of estrin are halted. The clitoris enlarges under the influence of androkinin (male sex hormone), but if thelykinin is given at the same time it fails to halt the masculinizing effect of the former, which indicates that the growth of the external genitalia is superseded by the male hormone. Thelykinin exerts a hysterotropic effect which is not retarded by androkinin. Somatic differentiation seems to be fundamentally female in the absence of any hormone at all, and that female differentiation takes place with or without the female sex hormone, but male characteristics are brought forth only under the influence of the male hormone. The cause of sex intergrades then, when explained upon such a basis would seem to lie in the effect of the stimulation of the soma by one hormone, the male. In the embryo this takes place whether the female sex hormone is present or not since the ovary is not necessary for female differentiation.

CONCLUSIONS

1. An unusual case of human ovotestis associated with a bisected uterus herniated into the inguinal canal has been described and analyzed.
2. Unique features are: the presence in each canal of a bisected uterus, fimbriated tubes, broad ligaments, and ovotestis.
3. The ovotestis was composed of ovarian and testicular tissue in the ratio of 3 to 1 (testicular).
4. Differentiation of the gonad had not gone on beyond the fetal period.

emphasized since the male or female sex hormone is not present to any great amount in the total absence of germinal material, that is, in the absence of follicles and seminiferous tubules.

Elsewhere, Simkins³ has called attention to the fact that the ovary is essentially a cortical, and the testis a medullary gland, whose components do not run a course in development that are strictly synchronous. The ovary arises first and develops in such a manner as not to encroach upon the testicular portion which begins its development later, and differentiates out of a blastema that is not identical with, but is in close association with the ovarian anlage. It would seem then, that the embryologic factors governing the differentiation of the gonads are by no means antagonistic but follow an orderly series of events. The testis differentiating later than the ovary and arising from material adjacent to it, which gradually encroaches upon the ovarian cortex and replaces it with testicular tissue rather than by converting the ovarian blastema into testicular elements. The primary differentiation of the gonad, forming its embryonic fundament, the so-called indifferent gland is, from this point of view, essentially ovarian stroma, which if not interfered with leads to female somatic differentiation. The "interference" at the end of the so-called "indifferent period" is not a parting of the ways at the crossroads, but a progressive differentiation which if advancing leads to maleness, and if not, to femaleness. Forward gonogenesis produces the testicle at a later date and as a direct result of continued female differentiation, by a process of replacement, rather than conversion, in which the linear factor of time plays an important role.

Speemann's organ formers exert their influence upon the early differentiation of the sexual anlage, but what influence they may exert upon the subsequent sexual differentiation can only be conjectured. The doctrine that sex determination and differentiation depends upon a chromosomal basis has been arrived at by a consideration of the end result rather than by noting the influence of the male and female sex chromosome upon the organism during the process of sex differentiation. The influence of the sex chromosome may be profoundly altered by the cytoplasm around it in which the hormones may be present and to which it must react. A strict chromosomal regimentation may have to be modified in the light of hormonal determiners which may work in harmony with the genes of sex and to some extent modify or control their influence.

The notion of linear differentiation is strengthened by the effects of injections of male and female hormones upon the lower animals. Wiesner⁴ has shown that female differentiation can, and does, go on in the absence of the female sex hormone. This lends support to the embryologic observation that if there is no interference with the embryologic development of the gonad it will first become an ovary. Of course we would expect, and we do find that female differentiation goes on, but to no decided extent when the female hormone is present, but the presence of the female hormone is not absolutely necessary for female differentiation.

of the latter two,^{60, 68} were obtained but did not agree with the cases as abstracted from Rosenblatt's⁵⁹ series. Two references^{51, 105} we were never able to find.

Our references were obtained from the *Quarterly Cumulative Index Medicus*, the *Index Catalogue of the Library of the Surgeon General's Office* in Washington, the *Quarterly Cumulative Index*, and the *Index Medicus*. The bibliography of each article was then searched for any further references. We are indebted to the Library of the Louisiana State University Medical School for its untiring efforts in obtaining the journals. The Surgeon General's Library at Washington, the John Crerar Library, Chicago, the New York Academy of Medicine, and the Orleans Parish Medical Society Library were our main sources.

To the best of our knowledge we have recorded every intraligamentary pregnancy of over seven calendar months that has been published, and present an additional case. We trust we have not missed too many.

CASE REPORT

A colored female of 39 years was admitted to the hospital Sept. 28, 1936, complaining of a mass in her abdomen of one year's duration. Her general health had always been excellent. Three full-term, normal pregnancies, and one five-months' abortion (not induced). Menses began at twelve, lasted three days, and occurred every four weeks. April 12, 1935: menstruated at her normal time, but the flow continued for six weeks; associated was a dull, suprapubic ache that never was severe or sharp. In July, 1935, she noticed a mass in her lower abdomen, and as amenorrhea had been present since April, the patient assumed she was pregnant. In October fetal life was felt. Pregnancy continued uneventful until the first part of January, 1936, when in the middle of the night, the patient was awakened with severe pains in the mid-epigastrium. The doctor in attendance believed that she was in labor. However, after forty-eight hours the pains ceased. At this time the patient noticed unusual activity of the infant which continued for two or three weeks, at which time all movement ceased; and there was marked engorgement of the breasts with lactation. A month and a half later she menstruated for three days, but amenorrhea continued until three months prior to admission, when her menses returned, were monthly, normal in amount and duration. The mass remained stationary in size from January, 1936, until admission.

On admission the patient appeared in excellent health and had no complaints. Examination revealed a large mass in the abdomen which extended from the pubis to a point halfway between the umbilicus and xiphoid. It was globular, smooth, semi-cystic, not tender, clearly demarcated and apparently not attached to the anterior abdominal wall. Vaginal examination revealed that the uterus was pushed to the left-anterior and was intimately adherent to the mass.

Wassermann was strongly positive, urine negative, sedimentation rate of thirty-five minutes. Blood chemistry: Blood urea, 14 mg. per 100 c.c. of blood, sugar, 80 mg. per 100 c.c. of blood.

A preoperative diagnosis was made of full-term abdominal pregnancy with dead fetus versus ovarian cyst. The unusual and suggestive history strongly indicated an extrauterine pregnancy.

Under subarachnoid analgesia, the abdomen was opened in the midline, incision extending from the symphysis pubis up to and beyond the umbilicus. Inspection revealed many fine adhesions between the tumor mass and the omentum and parietal peritoneum anteriorly, and to the sigmoid posteriorly. These adhesions were separated without undue difficulty. The mass was doughy in consistency with various

5. An explanation is offered for the cause of sex intergrades having its basis upon a monohormonic rather than a dihormonic system and that in the present case the male hormone was not powerful enough to force the embryologic development of the gonad completely out of the female or ovarian stage of differentiation into the complete somatic male.

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INTRALIGAMENTARY PREGNANCY

A SURVEY OF ALL PUBLISHED CASES OF OVER SEVEN CALENDAR MONTHS,
WITH THE DISCUSSION OF AN ADDITIONAL CASE

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IN THE fall of 1936, one of us (N. J. T.) operated upon a 39-year-old colored female for an intraligamentary pregnancy of eight and one-half months. The infrequency of this tumor warranted publication. The last investigation of this subject was by Remzy³⁷ in 1923. Unfortunately, he did not bring the literature up to date. We therefore attempted a complete survey and have recorded, according to year, in chart form all the cases reported.

The first article referring to intraligamentary pregnancy was by a German, Loschge¹ in 1816. He gave a beautiful detailed account of the autopsy findings of a young woman who died from rupture of an intraligamentary pregnancy at five and one-half months. His description of the anatomic relationship of the ovisac to the surrounding structures was most accurate and showed conclusively that this extrauterine pregnancy was developing in the broad ligament. Lawson Tait,⁸⁵ in his treatise on ectopic pregnancy in the late nineteenth century, convinced the medical profession of the possibility of this entity and in the year 1880 simultaneously with Maltakowsky⁹⁵ published reports of full-term intraligamentary pregnancies. In the following decade many additions were made. Sittner⁷⁰ in 1901 reported a series of 184 abdominal pregnancies, 39 of which were intraligamentary. Lemercier,⁹³ for his thesis, presented one case and added 18. Rosenblatt⁵⁹ in 1923 reviewed the literature from 1910 and out of 86 abdominal pregnancies, found 11 that were intraligamentary. One year later, Remzy³⁷ studied 30 cases in detail, placing particular emphasis on the disposal of the placenta. He was unable to reach any definite conclusions but stated that if possible the ovisac and placenta should be removed; however, conditions existing in the abdomen at the time of operation may alter the procedure. All these series contained many duplications which was fortunate, as Remzy's and Rosenblatt's abstracts frequently failed to afford us sufficient data. In spite of the duplications, and an earnest effort to locate the original articles, if the abstracts were scanty, the following cases could not be completed: Grimdale,¹⁰¹ T. Wilson,⁴³ Ruder,¹⁰² Immel,⁵⁹ and S. Fekete.⁵⁹ The original articles

ligament and the uterine vesicle fold. On opening the sac, a macerated fetus was found which measured 43 cm. in length. The placenta was of the trilobate type, and covered the entire sac. The uterus was enlarged to twice the normal size and continuous with the mass. The uterine wall throughout was of equal thickness and no opening existed between the uterine cavity and the ovisac. No evidence of the tube or ovary on that side could be found in spite of many sections.

The postoperative course was uneventful and the patient was discharged on the twelfth day.

DISCUSSION

Of the four possible types of full-term extrauterine pregnancy only one seemed to apply to this case. None of the four criteria for ovarian pregnancy was present. Its location, mode of origin, and peculiar relation to the uterus eliminated abdominal and tubal pregnancy. The relationship of the ovisac to the uterus appears to us to be of paramount importance, the continuity of tissue being explained by remembering that the ovisac after rupture into the folds of the broad ligament will lie in loose areolar tissue, which is limited by the relatively dense folds of the broad ligament and its attachments. As growth continues, these folds are further and further separated and the ultimate boundaries are the attachments of the broad ligament, which are: the uterus medially, the lateral wall of the pelvis, inferiorly the pelvic floor, and superiorly the tube at which site rupture frequently occurs. It thus seems certain that any true intraligamentary pregnancy near term must have these boundaries and accordingly appear continuous with the uterus anterior and posterior as the folds and peritoneum of the broad ligament fuse with the fibrous covering and peritoneum of the uterus.

The main source of blood supply must necessarily spring from the blood vessels supplying the uterus and those in the base of the broad ligament. However, additional supply could arise from any structure which might lie adjacent to the developing ovum. The omentum and intestine, particularly the sigmoid, would be the most likely sources.

We feel thus that a diagnosis of intraligamentary pregnancy cannot be made if this peculiar relationship between the uterus and ovisac does not occur. An abdominal pregnancy that becomes implanted in the culdesac could present at term an almost identical picture except for its relationship to the uterus.

PATHOGENESIS

Until recently it has been assumed that this entity resulted from the rupture of the tubal pregnancy into the broad ligament. Granting that this is true, certain conditions must be fulfilled to permit an ovisac to become secondarily implanted in the folds of the broad ligament.

1. Implantation must occur in that portion of the tube that is uncovered by the peritoneum, permitting extrusion of the products of conception into the potential space between the folds of the broad ligament.

firm areas and appeared to be arising from the right parietal wall of the pelvis. No plane of cleavage or demarcation existed between the mass and the uterus. As it appeared to be intraligamentary, it was believed that the easiest way to mobilize the tumor would be by removing the uterus retrograde and then separate the tumor from its attachment. The infundibulopelvic ligament on the left was



Fig. 1.—The left ovary, left tube, uterus, and broad ligament; the latter contain the ovisac before it was incised. This illustrates the continuity between the uterus and the tumor mass.

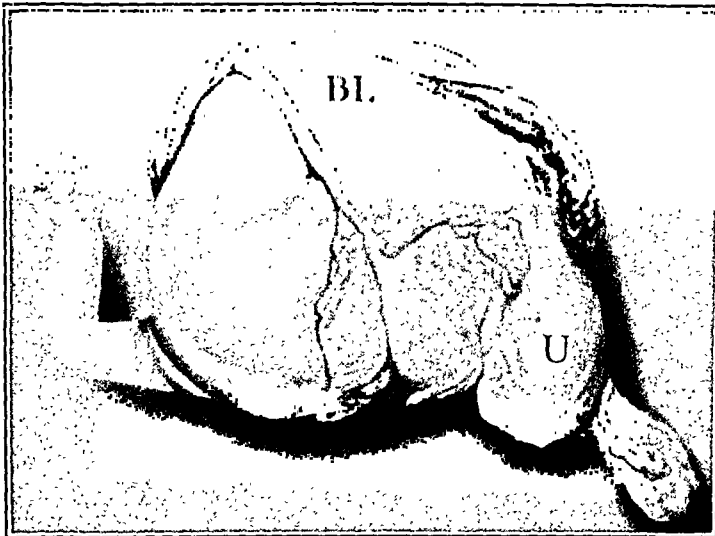


Fig. 2.—The fetus has been partially removed. *Bl.*, Broad ligament. *U*, Uterus.

therefore clamped and suture ligated, the broad ligament was severed in the avascular area down to the left uterine vessels which were clamped and severed. The uterus was then amputated at the level of the internal os and the right uterine vessels grasped and the entire mass with the uterus was then removed in toto. Some difficulty was encountered with the adhesions, but none with hemorrhage. The raw surfaces were peritonized with ease, utilizing the remaining portion of the broad

TABLE I

	YEAR	GESTATION MONTHS	FETUS	MOTHER	OPERATION	COMMENTS
Loschge ¹	1816	5½	D	D		Autopsy revealed rupture of sac with intestinal hemorrhage. Description of anatomy typical of intraligamentary
Lawson Tait ⁸⁵	1880	9	L	D	Marsupialization	Death 4th day P.O., exhaustion
Maltakowsky ⁹⁵	1880	9	L	L	Partial removal of placenta, packed	Ureter clamped with subsequent nephrectomy
Breisky ⁸⁷	1887	8	L	L	Total removal of placenta	
Spaeth ⁸⁸	1888	8	L	D	Marsupialization and tamponade, amniotic fluid fetid	Death following day, septicemia. Fetus died 24 hours
Taotman ⁸⁹	1888	8	L	L	Removal of sac and placenta, packed, drained, severe hemorrhage	
Eastman ⁹	1888	8	L	L	Removal of sac and placenta, drainage, glass drain	
Cullingworth ²	1888	7½	D	L	Total removal of placenta	Fetus dead 8 months, macerated
Negri ⁷¹	1898	8	L	L	Partial removal of placenta and sac, marsupialization	Fetus died from a malformation
Oliver ⁹²	1890	9	D	L	Marsupialization, amniotic fluid was purulent	Peritonitis. Fetus had been dead 5 months
Galabin ⁷²	1890	8	L	D	Marsupialization	Death second P.O. day, sepsis and hemorrhage
Voight ⁶⁷	1891	9	D	L	Total removal of placenta, partial marsupialization	
Schauta ⁹⁸	1891		D	L	Removal of sac and placenta	
Marchand ⁹⁷	1892	9	L	D	Marsupialization	Died following day. Autopsy showed bleeding from partially detached placenta
Rein ²¹	1892	9	L	L	Total removal of placenta, drained with glass drain	
Frommel ⁹¹	1892	8	L	L	Marsupialization and tamponade, profuse hemorrhage	Fecal fistula, closed spontaneously
Sippel ⁷⁴	1892	8½	L	D	Removal of sac and placenta	Death first day P.O., hemorrhage
Pan ¹⁰⁰	1893	9	L	L	Removal of sac and fetus	

2. This rupture must occur early in the life of the embryo before the trophoblast has lost its power to insure secondary nidation. This action is rapidly lost as they are soon transformed into well-formed villi.

3. The interval between primary and secondary implantation must be of short duration or else death of the fetus will occur. Whether the extrusion of the ovisac from the tube into the broad ligament should be gradual or rapid to promote optimal conditions for secondary growth is difficult to say. However, in the cases we reviewed, the frequency with which we have encountered a history of prolonged lower abdominal pain in the early months of gestation leads us to believe that this passage is slow. This pain, however, could be caused by the adaption and stretching of the broad ligament to its new occupant and not to the rupture.

Roxas and Villarama³⁸ observed that the trophoblastic cells rapidly develop into chorionic villi and that once this change has occurred, disruption of the primary implantation will result in death of the embryo. Accordingly they believe that secondary implantation is impossible and that in intraligamentary pregnancy the blastodermic vesicle burrows through the peritoneum and fascia of the posterior fold of the broad ligament into this potential space, where the loose areolar tissue is conducive to further growth and development.

Frankel and Schenck¹¹⁰ claim that endometrial tissue is a prerequisite to nidation. In their last article they state that in 14 out of 16 cases of ectopic pregnancies, endometrial tissue was present in the Fallopian tubes and explain their findings on the basis of Sampson's theory.

Believing that it is anatomically impossible for an ovisac measuring 5 or 6 cm. to rupture into the folds of the broad ligament, and that it is unlikely that a fertilized follicle would select for implantation the posterior layer of the broad ligament in preference to adjacent abdominal viscera or omentum, we think that a more plausible explanation of this phenomenon could be that this results from the development and growth into the folds of the broad ligament of a primary or secondary ovarian pregnancy, or a primary abdominal pregnancy implanted near this site, by the same mechanism that cysts of the ovary become intraligamentary.

We further believe that rarely is a full-term pregnancy or a large cyst completely enclosed in the folds of the broad ligament. As growth is rapid, thinning and attenuation of the broad ligament occurs so quickly that rupture is inevitable. This can account for the frequency of the many adhesions of the ovisac on its medial and superior border to adjacent viscera. Just recently we have encountered several very large ovarian cysts that were intraligamentary and over three-fourths of the cyst walls were covered only by a thin layer of peritoneum, the limits of the broad ligament being easily discernible. In many of the recorded cases mention was made of the inability to peritonize the wound. In true intraligamentary cysts or pregnancies this difficulty is never encountered as a peritonized broad ligament is in abundance.

TABLE I—CONT'D

	YEAR	GESTATION MONTHS	FETUS	MOTHER	OPERATION	COMMENTS
Rodiger ²²	1906	9	D	L	Packed with iodoform gauze	Fetus macerated
Tissier, Wiart ⁴¹	1908	8	L	L	S.V.H., total removal of placenta, drainage	
Lobenstine ³⁴	1908	8	D	D	Total removal of placenta, packed, marsupialized	Died few hours P.O. hemorrhage and shock
Tissier, Penard ⁴⁰	1909	9	D	D	Marsupialization, uterus ruptured, cause?	Death following day. Fetus macerated
G. D. Nutt ⁶¹	1910	9	D	L	S.V.H., removal of sac and placenta	Fetus macerated, dead 2 years
Gitelson ⁶⁹	1910	8½	D	D	Total removal of placenta, marsupialization, drainage	Died sixth day, P.O. peritonitis
Grimdale ¹⁰¹	1910	9	D	L		
MacPherson ³⁵	1911	9	?	L	Hemorrhage prevented removal of placenta, packed	Phlebitis
Scipiades ³⁰	1911	9	D	L	Removal of sac and placenta	Fetus macerated
Velitz ⁶⁶	1911	8	D	L	S.V.H., total removal of placenta, resection of intestines	
Immel ⁵⁹	1912	9	L	L		
N. L. Hood ⁶²	1913	9	L	L	Partial removal of placenta, marsupialization, drainage	
S. Fekete ⁶⁹	1913	9	D	L		
T. Wilson ⁴³	1913	9	D			
Engelking ³¹	1913	8	D	L	Removal of sac and placenta	Fetus macerated
Stoeckel ⁹⁴	1916	9	-	-	Total removal of placenta	Drained through cul-de-sac
Marriott ³⁶	1918	9	D	L	Total removal of placenta	Fetus macerated. Dead for 8 months
Kuncz ⁶⁵	1919	9	D	L	S.V.H., removal of sac and placenta	
Ruder ¹⁰²	1919	9	D	L		
Ellison ⁴⁹	1922	9	D	L	Total removal of placenta, no drainage	Sinus closed 100 days P.O.
Roxas, Villarama ³⁸	1924	9	L	L	Partial removal of placenta, abdominal drainage	
Remzy ³⁷	1924	7	D	L	Total removal of placenta, packed	Phlebitis, pulmonary embolus. Fetus macerated
Thompson ⁵⁰	1928	8½	D	L	Partial removal of placenta	Toxemia of pregnancy. Intestinal obstruction 2 mo. later

TABLE I—CONT'D

	YEAR	GESTATION MONTHS	FETUS	MOTHER	OPERATION	COMMENTS
Lusk ⁷⁵	1893	7	D	L	Tamponade	
Hofmeier ⁷⁶	1893	9	D	L	Partial removal of placenta, marsupialization, tamponade	
Tauffer ⁷³	1893	7	D	L	S.V.H. with removal of sac and placenta	
Griffith ¹³	1893	9	D	L	Removal of sac and placenta, drainage, glass drain	
Herff ⁷⁷	1895	8½	L	L	Removal of sac and placenta	Fever, thrombophlebitis
Hardie ⁷⁸	1896	8	D	L	Marsupialization	
Galabin ¹²	1896	9	D	L	Removal of sac and placenta and ovarian tumor	Fetus dead 21 years and macerated. Braxton Hicks had diagnosed 21 years before
Dunning ⁷	1897	8	D	L	Removal of sac and placenta	
Rokitansky ⁷⁹	1898	8½	L	L	Partial removal of placenta with tamponade	
Rochet ⁹⁶	1898	9	D	L	Evacuation of sac	Placenta removed 7th day P.O. Fetus macerated
Martin ¹⁸	1899	8	D	D	Removal of pelvic organs in toto, drainage abdomen and vagina	Died, day? Fetus macerated
Donald ⁶	1899	7	Died at C.R.	L	Packed. Fetus extracted by vagina	
Jayle, Delherm ¹⁶	1900	9	D	L	Marsupialization	Fetus macerated, dead 7 months
Cragin ⁸⁰	1900	8	L	L	Tamponade	
Menge ⁸¹	1900	8	D	L	S.V.H., removal of sac and placenta	
Borysowicz ⁸²	1900	8	L	L	Marsupialization	Placenta removed 6 weeks P.O.
Cragin ⁸³	1900	8½	L	L	Removal of sac and placenta	
Lemercier ⁶³	1900	9	D	L	Marsupialization	Fetus dead 8 months and macerated
Sneguireff ⁸⁴	1900	8½	L	L	Partial removal of sac and placenta. Marsupialization. Tamponade	
Skutsch ⁸⁶	1902	7		L	Marsupialization, hemorrhaged and packed	
Lyle ¹⁷	1906	9	D	L	Attempt made to remove placenta, unsuccessful	Fetus macerated, 18th P.O. day, colpotomy

expected as operative technique and asepsis are improved. Of the 10 maternal deaths, 5 were due to hemorrhage. In 3 of the 5, a living child was obtained, the other 2 being dead, but not macerated. This association of hemorrhage with a living newborn is significant, and is to be remembered when an attempt is made to remove a placenta with evidence of bleeding from the placental site. In these cases it is much safer to evacuate the sac and close the abdomen. The placenta will be readily absorbed.

TABLE II. COMPARISON BY DECADES OF MATERNAL AND FETAL DEATHS

	1880 1889	1890 1899	1900 1909	1910 1919	1920 1929	1930 1937	TOTALS
Number of cases	8	21	13	10†	4*	6	62*††
Number of maternal deaths:	2	4	2	1	0	1	10† or 16%
Sepsis	1	1		1		1	4
Exhaustion	1						1
Hemorrhage		3	2				5
Number of fetal deaths:	1	13	7	7†	4	5	37†† or 58%
Macerated	1	4	5	4	1	4	19
Prematurity		3					3
Not stated		6	2	3	3	1	15

*Magid's case omitted.

†Five cases omitted as records incomplete. Grimdale,¹⁰¹ Immel,⁵⁹ S. Fekete,⁵⁹ T. Wilson,⁴³ Ruder.¹⁰²

‡Cases of Loschge¹ and Toth³⁷ not included.

FETAL MORTALITY

The fetal mortality was 58 per cent and a little over half of the dead fetuses were macerated. In several cases the fetus had been retained with no apparent injury to the mother for many years; ten years in Hardy's case and twenty-one years in the case of Galabin. The latter is interesting as the patient had formerly been under the care of Braxton Hicks, and was diagnosed in 1872 as a full-term extrauterine pregnancy. Conservative therapy was advised, and twenty-one years later a rapidly growing ovarian cyst necessitated operation due to the pressure symptoms.

OPERATIVE PROCEDURES

The operative procedures (Table III) of tamponade and packing were isolated but probably belong under the same heading. It is also clear that it is impossible to pack without draining. Since 1910, the incidence of marsupialization has greatly diminished. In recent years, if the ovisac and placenta could not be removed the abdomen has generally been closed without packing or marsupialization. There has also been a tendency, however, to remove the placenta in every case. This is regrettable as the retained placenta is readily taken care of, and removal frequently produces an uncontrollable hemorrhage.

TABLE I—CONT'D

	YEAR	GESTATION MONTHS	FETUS	MOTHER	OPERATION	COMMENTS
Magid ⁵²	1928	8	D	L	Diagnosis of intraligamentary is questionable	Toxemia of pregnancy
McLennan ⁵³	1931	8	L	D	Removal of sac and placenta	Died 16 days P.O. peritonitis and nephritis
Ware ⁵⁷	1934	9	D	L	Partial removal of placenta, packed	P.O. sinus 6 wk. with temperature 4 weeks. Fetus macerated
Ware ⁵⁷	1934	9	D	L	Total removal of placenta, packed and marsupialized	Fetus macerated
Cernoeric ⁵⁸	1935	9	D	L	Total removal of placenta, packed, drained	
Tessitore, Champion	1936	8½	D	L	S.V.H., L.S.O., removal of sac and placenta, no drainage	Fetus macerated, dead 10 months
R. W. Hardy ⁵⁹	1937	8	D	L	Removal of sac and placenta. No drainage	Fetus calcified, dead 10 years
Toth ³⁷	Be- fore 1924	9	-	-	Removal of sac and placenta	

INCIDENCE

We have previously described the structural relationship that we believe must exist between the body of the uterus and the ovisac before one is justified in arriving at the diagnosis of a broad ligament pregnancy. With several exceptions there is little reference in the operative procedure of the many cases reported that would enable one to study the literature from this angle. This is unfortunate from a statistical viewpoint and prohibits arriving at any conclusion regarding the true frequency of this entity. Kennedy⁴⁹ estimated that one out of every 613 cases of ectopic pregnancy is intraligamentary. He derives this ratio from the statistical reports of Sittner,⁷⁰ Rosenblatt,⁵⁹ Farrar,¹⁰⁶ Lewis,¹⁰⁷ Luker,¹⁰⁸ Mason and Storro,¹⁰⁹ and Williams.¹⁰⁴ It is generally accepted that ectopic pregnancy occurs about once in every 200 pregnancies and that the ratio of abortion to pregnancy is one to two. From these figures it may be estimated that out of every 183,900 pregnancies, one will be intraligamentary.

To facilitate the analyzing of the cases reported, we divided them into decades for comparison.

MATERNAL MORTALITY

The maternal mortality was 16 per cent (Table II) and showed a tendency to decrease with each decade. This is to be more or less

one operator with this entity. However, we feel six to eight weeks should be allowed to elapse, and no difficulty should then be encountered with hemorrhage in removing the sac and placenta. Dense adhesions to vital organs may likewise prevent complete removal, but this should not be encountered in intraligamentary pregnancy with the frequency found in abdominal cases.

CONCLUSIONS

1. An attempt was made to present a complete survey of the literature of the intraligamentary pregnancies of over seven calendar months with the discussion of an additional case.

2. The anatomic relationships necessary to diagnose an extrauterine pregnancy were discussed. Special emphasis was placed on the complete continuity of the uterus and the ovisac, anterior and posterior, and the absence of any line of demarcation.

3. Treatment was outlined. If the infant is viable, operation with conservative handling of the placenta is indicated. If the fetus is dead, operation should be deferred six to eight weeks until the placental circulation has atrophied.

4. A suggestion was made as to the origin of this type of pregnancy.

5. Intraligamentary pregnancies occur once in every 183,900 pregnancies.

We are indebted to Dr. Peter Graffagnino for his kind help and many valuable suggestions and to Dr. Charles Midlo, whose excellent cooperation in translating the publications of the German and allied tongues made this survey possible.

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TABLE III. COMPARISON BY DECADES OF OPERATIVE PROCEDURES

	1880 1899	1890 1899	1900 1909	1910 1919	1920 1929	1930 1937	TOTALS
Number of cases	8	21	13	10†	4*	6	62*††
Operative procedures							
Marsupialization	3	7	7	2		1	20
Partial removal of placenta	2	2	1	1	2	1	9
Total removal of placenta	2	2	1	3	2	2	12
Tamponade	1	4	3				8
Removal of sac and placenta	2	7	1	2		2	14
Packed	2	1	3	1	1	3	11
Drained	2	3	1	2		1	9
Hysterectomy with removal of sac and placenta		2	2	3		1	8
Evacuation of sac		1	1				2
Resection of intestines				1			1
Total number of operative pro- cedures	14	29	20	15	5	11	94

*Magid's case omitted.

†Five cases omitted as records incomplete. Grimdale,¹⁰¹ Immel,⁵⁹ S. Fekete,⁵⁹ T. Wilson,⁴³ Ruder.¹⁰²

‡Cases of Loschge¹ and Toth³⁷ not included.

DIAGNOSIS

The diagnosis of full-term extrauterine pregnancy has recently been excellently presented in papers on abdominal pregnancy, so we will not discuss this in detail. Recognition of this condition requires alertness on the part of the examiner, but a careful history and physical and vaginal examinations under general anesthesia, if necessary, should enable one to recognize this entity in the majority of cases. In our patient the uterus could be palpated separate from the tumor. If the indications are present, exploration of the uterine cavity will clinch the diagnosis. An x-ray of the abdomen will demonstrate (1) a fetus which appears higher than normal, (2) faulty or no engagement, and (3) abnormal presentations.

TREATMENT

This depends upon the viability of the infant.

1. *Viable Fetus*.—Operation is indicated. Type of operation will vary with findings. Ideally, removal of the sac and placenta should be performed. If the placenta is attached to any viscera from which it cannot be readily freed or if it is evident that difficulty will be encountered with bleeding, the best results will be obtained if the placenta and sac are left in situ. If the mother has several children or has no desire for further progeny, or if it is technically difficult to remove the ovisac without the uterus, the latter may have to be sacrificed. If drainage is thought advisable, the vaginal route is preferable.

2. *Dead Fetus*.—With absence of infection, operation should be deferred until the fetal circulation has sufficiently atrophied that the danger of hemorrhage is reduced to a minimum. The length of time necessary to enable these retrogressive changes to occur is difficult to determine, due to paucity of material and limited experience of any

OBSERVATIONS ON INTRAUTERINE PRESSURE DURING FIRST STAGE OF LABOR

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THE evaluation of intrauterine pressure has been a problem of much interest and much speculation. Most of the older observers have been content merely with attempts to determine the tension of the amniotic sac and the amount of expulsive force of the uterus, with the aid of the abdominal musculature. Accordingly, I have performed a number of experiments on patients in labor, making use of a Voorhees bag and a specially designed pressure recording apparatus. From these experiments I have compiled a series of tabulations and data which seem to me to be indicative of the true intrauterine pressure.

Poppel in 1863 thought that a study of the resistance of the fetal membranes would permit him to draw approximate conclusions with regard to the total pressure exerted by the uterine contractions on the uterine contents. Duncan in 1869 thought that the tensile strength of the amniotic membrane alone sufficed to give an indication of the amount of pressure necessary to rupture membranes.

A critical study of the work done by both of these men shows that neither one of them simulated or even approximated physiologic conditions. The membranes were firmly fixed to the margins of the vessels used and because of this the inherent elasticity of the membranes was not given free range as normally occurs. Both directed the testing force against a small area of membrane, and they were content to measure this force as representative of the true uterine pressure.

Schatz who was the first to use internal hysterography in the study of the dynamics of the uterus found the intrauterine pressure before the onset of labor and between the labor pains to be equal to 20 mm. of mercury. This pressure he called the pseudo intrauterine pressure. During labor pains the height of the column of mercury varied from 80 to 250 mm. of mercury. These readings were obtained throughout the course of an entire labor and no attempt was made to remove or account for the accessory forces which come into play during the second stage of labor and because of this, these readings are not indicative of a true intrauterine pressure.

Westermarck in 1893 showed that at the beginning of labor the pressure was about 20 mm. of mercury while at the height of the pain the pressure recorded varied greatly up to 168 mm. of mercury. His observations were carried through the second stage of labor.

Weilock, in a recent paper on the measurement of the pressure in the hydramniotic uterus, brought out conclusive data showing that in the normal pregnant uterus before the onset of labor the pressure is practically nil. His experiments were performed by inserting a cannula through the abdominal and uterine wall into the amniotic sac.

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DESCRIPTION OF APPARATUS

The apparatus consists of a stand with a mercury manometer (Fig. 1). The manometer is so fixed that it can be raised or lowered according to the level of the Voorhees' bag inserted in the uterus. Fluid is forced out of the bag in accordance with the amount of pressure exerted. This in turn is transmitted through a column of air to a column of mercury on a millimeter scale. The difference in the level of the column of mercury is taken as a measure of the force of the uterine contraction.

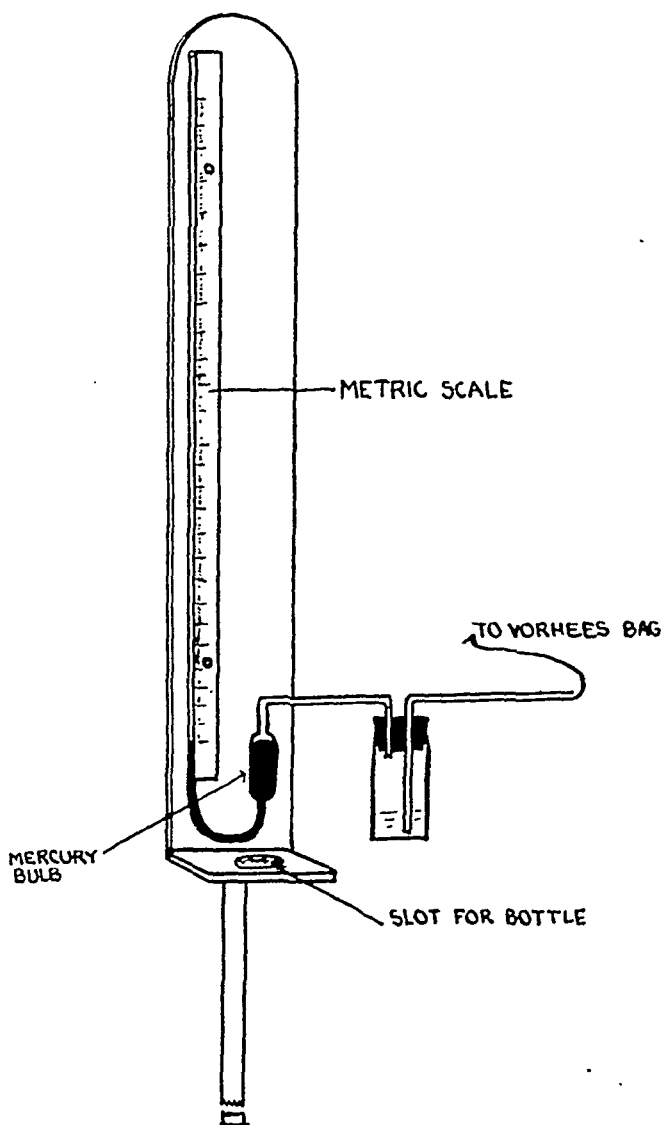


Fig. 1.

CONSIDERATION OF CASES

In the selection of cases for the determination of the intrauterine pressure, only those patients were selected in whom there was no contraindication to the insertion of the Voorhees' bag. Labor was allowed to occur spontaneously, no traction was applied to the bag in order that the lower uterine segment would not be thinned out except by pressure exerted by the uterine contractions. The record-

FORCES CONCERNED IN LABOR

As long as the membranes are unruptured during the first stage of labor, whatever force is exerted by the contracting musculature of the uterus is transmitted to the liquor amnii and by it to the fetus. In accordance with the laws of fluid pressure, it is transmitted equally in all directions and since the lower uterine segment and the cervix offer the least resistance we have a resultant stretching of the lower uterine segment and a dilatation of the cervix. If the above can be assumed to be true, there is no reason to believe that the fetus should exert pressure on the lower uterine segment, but if it does, it is not in excess of that exerted by the uterus on the amniotic fluid.

With regard to the pressure of the abdominal wall we may say that it exerts no pressure on the abdominal organs unless the abdominal musculature is voluntarily contracted. However, during labor, when the cervix has retracted and the presenting part lies on the perineal floor, the abdominal muscles reflexly come into play and the patient bears down. At this time, the expulsive force on the uterine contents is a combination of the uterine muscular contractions and the contractions of the abdominal musculature. Prior to this time and before the cervix is completely dilated, there is no tendency on the part of the patient to bear down unless she is so instructed by the attendant or else thinks that by bearing down she may hasten the completion of labor. From this it can be assumed that prior to complete dilatation or when the presenting part is on the perineum, the pressure exerted on the uterine contents is derived exclusively from the uterine musculature during their contractions. To attempt to differentiate just how much is due to accessory muscle action is a problem worthy of consideration.

In the series of cases presented in this paper, all of which except one were full term, a large Voorhees' bag was inserted into the uterus prior to the onset of labor and then the bag was filled with approximately 800 c.c. of a 1:3,000 bichloride solution. The diameter of the base of the bag was 11 cm. The presenting part was kept out of the pelvis until the cervix was completely dilated by the size of the bag. In all cases care was taken not to rupture the amniotic sac. The free end of the Voorhees bag was then connected to a specially constructed manometer and readings were taken from the beginning of labor until complete dilatation of the cervix. The introduction of the bag into the uterus and its subsequent filling with bichloride solution itself created a pressure, then again the increase in uterine contents served to increase the pressure inside the uterus. The pressure so created has been designated the standing uterine pressure. The difference in pressure between the standing pressure and the pressure obtained during a uterine contraction has been designated the relative intrauterine pressure.

cepting the nose and mouth, was immersed in a basin of water and the volume of fluid displaced measured, which in this case was 2,900 c.c. Thus, the total volume of the uterine cavity was found to be 3,950 c.c.

All the remaining cases have been handled in the same manner; the data obtained tabulated and recorded in chart form. Case 1 in Table I corresponds to Case 1 in Table II, etc.

TABLE I. LENGTH OF LABOR WITH BAG INDUCTION

CASE	AGE	PARA	MCDON- ALD CM.	CERVIX		INSERTION OF BAG	ONSET OF LABOR AFTER INSERTION OF BAG	LENGTH OF LABOR
				DILATA- TION CM.	THICK- NESS CM.			
1	21	i	35	3.0	0.5	11:45 A.M.	4 hr. 45 min.	2 hr. 20 min.
2	21	i	33	2.5	0.5	12:00 M.	1 hr. 19 min.	4 hr. 3 min.
3	18	i	34	2.0	1.0	10:30 A.M.	2 hr. 30 min.	8 hr. 30 min.
4	26	vi	31	2.5	0.5	10:30 A.M.	2 hr. 15 min.	2 hr. 25 min.
5	30	v	39	2.5	1.0	2:30 P.M.	1 hr. 56 min.	2 hr. 15 min.
6	22	i	35	2.0	0.5	9:45 A.M.	9 hr. 41 min.	5 hr. 4 min.
7	23	i	29	2.5	1.0	9:30 A.M.	2 hr. 55 min.	13 hr. 45 min.
8	20	i	36	3.0	1.0	10:00 A.M.	3 hr. 35 min.	3 hr. 57 min.
9	19	i	36	2.5	1.0	10:30 A.M.	2 hr. 10 min.	5 hr. 24 min.
10	19	i	36	2.5	1.0	10:00 A.M.	3 hr. 30 min.	5 hr. 50 min.
11	18	i	33	2.0	1.0	1:15 P.M.	4 hr. 7 min.	4 hr. 54 min.

TABLE II. RELATION OF PRESSURE TO VOLUME OF UTERUS AND NUMBER OF PAINS

CASE	VOLUME OF FETUS C.C.	VOLUME OF PLA- CENTA C.C.	VOLUME OF FLUID C.C.	TOTAL VOL- UME C.C.	LENGTH OF LABOR	NUM- BER OF PAINS	MAX- IMUM PRES- SURE MM.	MIN- IMUM PRES- SURE MM.	AVERAGE PRES- SURE MM.
1	3025	575	555	4155	2 hr. 20 min.	37	92	12	41.3
2	2900	580	470	3950	4 hr. 3 min.	75	125	8	43.3
3	3775	650	600	5025	8 hr. 30 min.	195	80	7	24.6
4	2300	470	395	3165	2 hr. 25 min.	85	65	9	23.1
5	3000	550	480	4030	2 hr. 15 min.	48	45	10	22.3
6	3300	510	455	4265	5 hr. 4 min.	153	50	10	28.7
7	2100	250	435	2785	13 hr. 45 min.	164	54	13	35.4
8	4050	750	850	5650	3 hr. 57 min.	104	43	8	23.2
9	4000	690	350	5040	5 hr. 24 min.	70	47	11	31.7
10	2300	525	610	3435	5 hr. 5 min.	139	72	9	27.6
11	2750	500	525	3775	4 hr. 54 min.	58	75	12	49.9

By a careful study of the tables, it can be seen that the duration of labor in all these cases, with the exception of one case, was much shorter than in the average spontaneous case. Only the first stage of labor is being studied. Attention is directed to this fact because the pressure created by the uterus should be greater if the duration of labor is shorter than normal. The time required to dilate the cervix is taken as a criterion of the greater pressure in the shorter labor. As a matter of interest and that there may be a basis of comparison, two multiparous patients were used in our experiments. These are represented in the tables as Cases 4 and 5. The average duration of labor in the primiparous patients was four hours and fifty-one minutes; in the multiparous patients it was two hours and twenty minutes.

ings began at the onset of labor and were continued throughout until complete dilatation of the cervix occurred. Frequent rectal examinations were made to determine when the cervix was completely dilated. As soon as this occurred, the fluid was allowed to drain out and the bag removed. In one case the bag was allowed to be expelled by the uterus and accessory forces in order that a comparison might be drawn between intrauterine pressure and pressure exerted by the abdominal musculature in the process of bearing down.

PRESENTATION OF DATA

Presentation of each case in detail is impractical, therefore several will be presented in graph form, as the entire course of labor during the first stage can be graphically represented. Other cases will be presented in chart form.

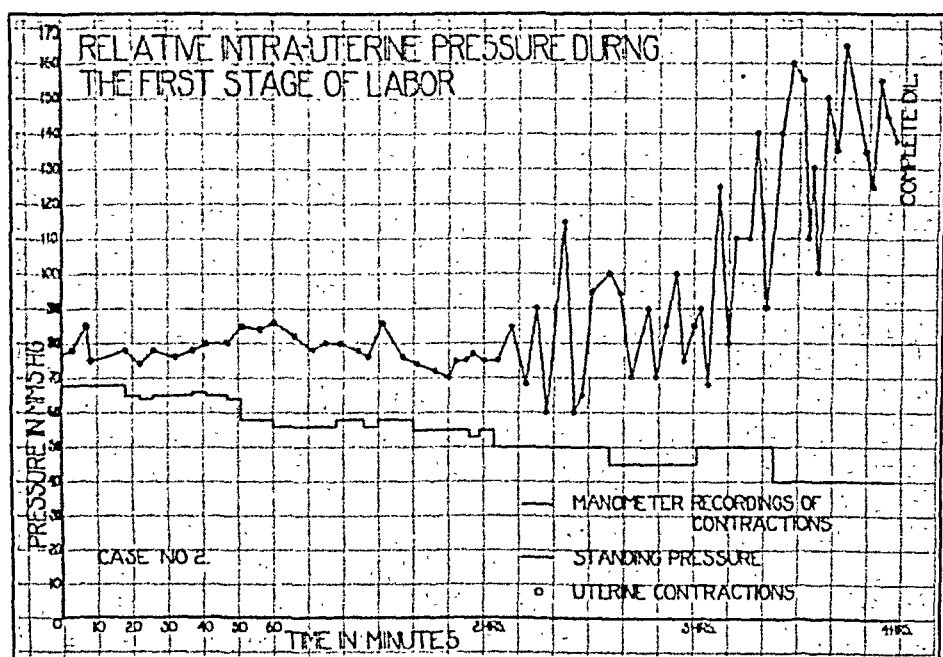


Fig. 2.

The graph of Case 2, a primipara, shows the elevations of the mercury manometer readings over the standard pressure readings for each pain (Fig. 2). The time of onset of each contraction in relation to the previous as well as to the following contraction is also shown. From the graph it will be clearly seen that as the first stage of labor nears completion the relative intrauterine pressure values increase, while the standard pressure values decrease as the first stage nears completion. The decrease in standing pressure is explained by the fact that as the first stage of labor nears completion the Voorhees' bag is gradually being pushed out of the cervix thus decreasing the uterine contents.

This case was selected because it showed the maximum value of relative pressure obtained in the series. During the course of delivery all the amniotic fluid was collected in a basin and the volume measured. In this case the volume was 470 c.c. The placenta and membranes were measured according to the volume of water which they displaced and were found to be 500 c.c. In a similar manner the fetus, ex-

The graph of Case 5 (Fig. 3), a multipara, shows that the duration of the first stage of labor is much shorter and that the relative pressure values are not as great as in the primipara.

The graph of Case 9 (Fig. 4) represents the case in which the membranes were ruptured purposely in order to note the effect on relative pressure values. It will be seen here that the contractions seem to maintain approximately the same intensity throughout the entire first stage of labor. Whether this was due to the fact that the membranes were ruptured or whether it was just a peculiarity of this particular case was not determined.

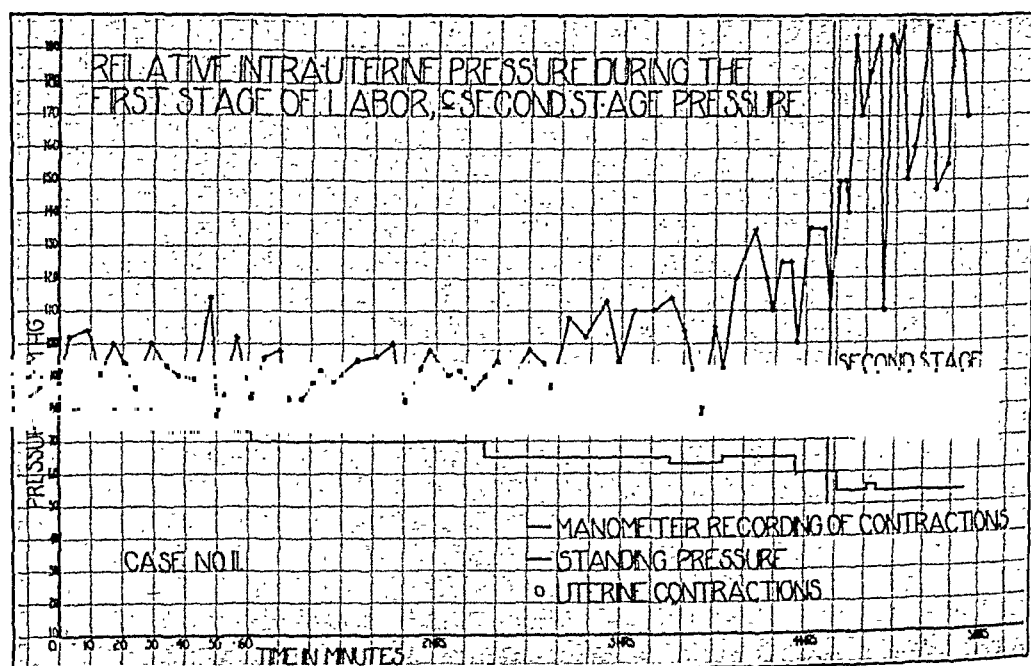


Fig. 5.

The graph of Case 11 (Fig. 5), a primipara, is the one in which the Voorhees' bag was allowed to remain in the vagina throughout the second stage of labor, so as to show more clearly the greater pressure exerted during the second stage.

OBSERVATIONS OTHER THAN THOSE DEALING WITH THE PLAN OF WORK

The use of the Voorhees' bag has made possible certain incidental observations on the effects of the intrauterine bag on uterine contractions and the course of labor.

Normally, in the beginning of spontaneous labor the contractions are usually weak and irregular. In this series of cases, the period of weak and irregular contractions has been markedly shortened, hence the duration of the first stage of labor has been shortened in almost all of these cases.

The character of the contractions in this series also shows some interesting features. The time from the onset of the contraction up

Table II presents data relating to the volume of the uterus, the length of the labor, and the number of pains in comparison to the average relative pressure values obtained during the course of the first stage of labor. This chart brings out the fact that the volume of the uterus is not related to the number of pains nor to the length

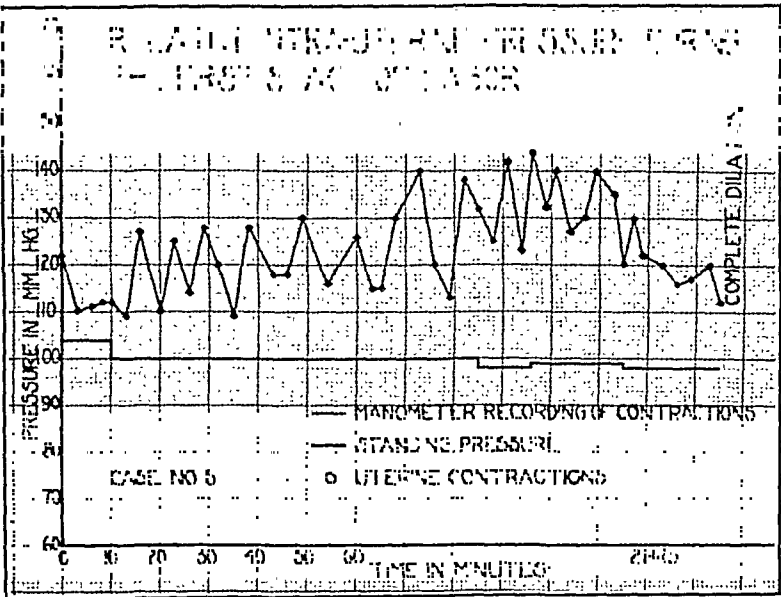


Fig. 3.

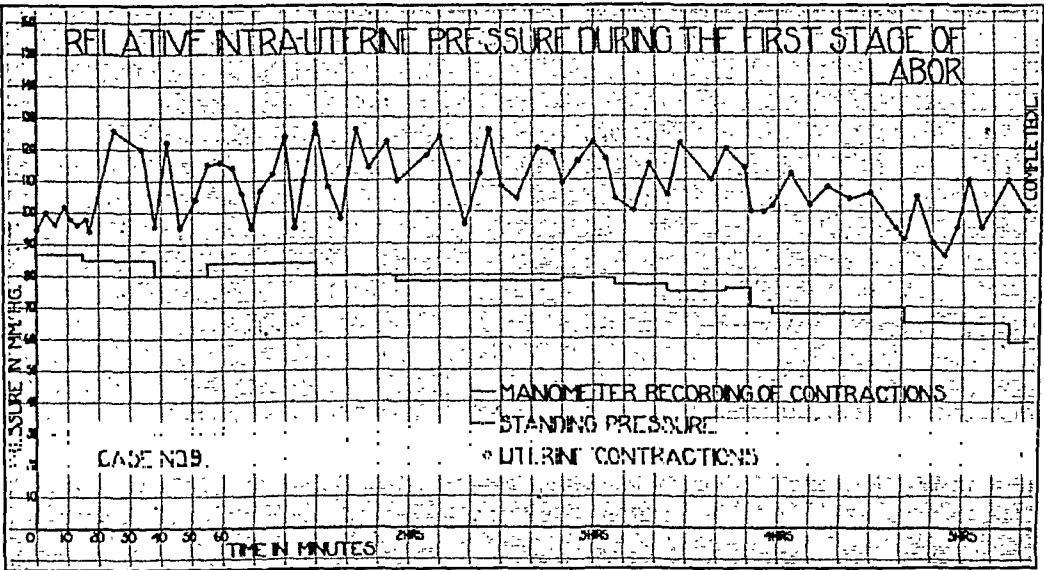


Fig. 4.

of the labor. It shows rather conclusively that in those labors with fewer pains during the first stage, the average relative pressure values obtained were greater. This is true of the primiparous patients only, as in the two cases of multiparas, the average relative pressure values were the lowest in the series even though the average length of those labors was only two hours and twenty minutes.

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1020 MEDICAL ARTS BUILDING

CYSTIC ENDOMETRIAL CHANGES IN OVULATORY CYCLES* THE MIXED ENDOMETRIUM

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INCLUDED in our collection of over 1,000 endometrial biopsy specimens secured at various phases of normal and abnormal menstrual cycles are five that do not conform to the usual cyclical variations originally described by Hitschmann and Adler. On the contrary these specimens present a *mixed* histologic picture containing characteristics of both the proliferative (cystic) and the secretory phases at a time when only secretory characteristics should be evident. This combination does not appear to have been noted heretofore.

The endometrium during the normal menstrual cycle goes through a series of changes dependent upon a concomitant cycle of events in the ovary. The follicular hormone† dominates the first half of the cycle and stimulates the proliferation of the endometrium. During this stage the endometrium is characterized by the presence of narrow straight nonsecreting glands lined by pseudostratified epithelium and by a dense stroma composed of deeply staining spindle cells.

Following ovulation the ruptured follicle is transformed into a corpus luteum, and the latter produces a hormone called progesterone. Al-

*Read at a meeting of the Bronx Pathological Society, January 19, 1937.

†Since the various estrogenic hormones have been isolated in crystalline form, and their chemical structure identified, it becomes possible to designate them by their chemical names. The dosage may be stated in milligrams when a pure hormone preparation is used. The hormone which is secreted by the follicle is estradiol. This hormone is then excreted through the urine as estrone (or theelin, estrin, progynon) and estriol (or theelol). Amniotin and emmenin are mixtures of estrogenic compounds. It is advisable, whenever possible, to substitute milligrams or gamma (1 mg. = 1000 gamma) for the rat or mouse unit. The biologic unit varies greatly, depending upon the numerous conditions which influence the method of standardization, while a milligram of hormone remains the same quantity under all conditions. Many investigators have accepted 1 rat unit to be the equivalent of 5 gamma of crystalline estradiol benzoate. Because of the rapidity with which estradiol is excreted, it is usually coupled with benzoic acid to form an ester (the phenolic benzoate is commercially known as progynon-B). The mouse unit varies from about 0.04 gamma to 0.1 gamma of pure estrone depending upon the procedures employed in the different laboratories. The ratio between the rat and mouse units is somewhere within the limits 1:4 to 1:9.

With the advent of crystalline corpus luteum hormone, progesterone, 1 mg. of the hormone is equal to one International Unit. One Clauberg Unit is the equivalent of 0.5 mg., and one Allen Unit is the equivalent of 1 mg. of crystalline progesterone.

to the time when it reaches its maximum was very short, varying from fourteen to eighteen seconds. The contraction was maintained at its peak for four to eight seconds and then there was a gradual fall to the standing pressure. This last phase of contraction was longest, lasting from twenty-two to twenty-eight seconds.

It was found that the manometer recorded the contraction before the patient was aware of pain. The patients complained of the pain just a few seconds before the contraction had reached its maximum and ceased to complain several seconds before relaxation was complete. It was also observed that there was no definite uniformity in intensity of successive contractions; one strong contraction might be followed by another strong contraction or even a weaker or stronger contraction. There was throughout the entire first stage a rather definite regularity in the occurrence of contractions but occasionally a second contraction set in before there was complete relaxation from the first contraction.

Almost invariably there was a slowing of the fetal heart rate while the contraction was at its height; this slowing was followed by a temporary increase in rate during the interval between contractions.

SUMMARY AND CONCLUSIONS

1. Although the artificial apparatus described in this paper may have some inaccuracies, yet by its use much valuable information concerning uterine pressure has been obtained.

2. From the values obtained, it can be said that the intrauterine pressure bears no relationship to either the volume of the uterus or the amount of amniotic fluid.

3. In primiparas, the intrauterine pressure seems to be inversely proportional to the duration of the labor.

4. Evidently the pressure created by the accessory powers of labor is transmitted directly to the fetus through the uterine wall because of the much greater pressure values obtained during the second stage of labor.

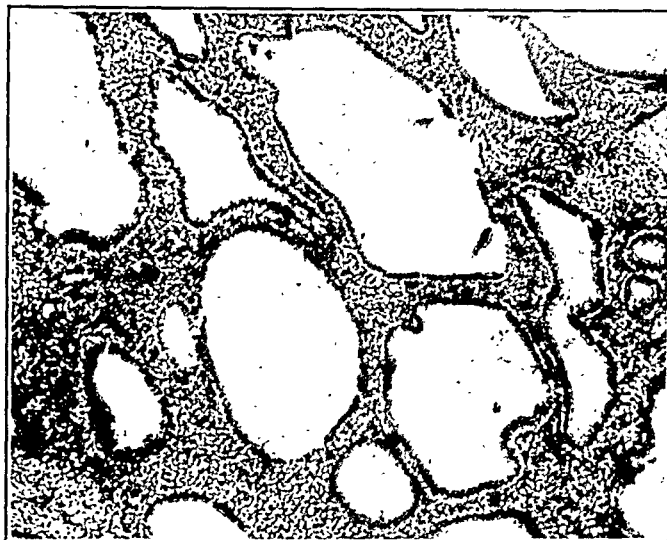
5. From this series of cases the total average relative intrauterine pressure value was 32.1 mm. of mercury. The maximum average was 49.9 mm. of mercury. In each case the average relative intrauterine pressure was obtained by adding all the pressure values for each pain and then dividing by the number of pains. The averages were then added and the total divided by the number of cases giving the total average value.

6. The relative intrauterine pressure value in this series did not exceed 125 mm. of mercury.

7. The occurrence of several superimposed, severe contractions could produce a slowing of the fetal heart rate sufficiently to cause anoxemia of the fetus with resulting fetal asphyxia. This may explain in a measure the fetal mortality during the first stages of labor.

came regularly every twenty-eight days, but the flow was now of one to two days' duration and scanty in amount. In 1934 the prolonged cycle returned but the short scanty flow persisted.

The last regular period was Feb. 12 to 13, 1935. Beginning April 13, 1935, she stained until April 27, 1935, when a biopsy was taken. This revealed a typical cystic endometrium. One week later (May 4, 1935) biopsy again showed a cystic



A.



B.

Fig. 1.—Case 1. (A) Mixed endometrium. Amenorrhea for two months followed by two weeks' bleeding. Cystic endometrium contains some secreting glands. (B) Actively secreting gland (high power).

endometrium (Fig. 2) but the stroma cells were now pale and large and closely resembled those of the secretory phase. A secretory epithelium was not present, however. The patient had what she described as a "regular period" on May 12 to 14, 1935.

The following three periods occurred at twenty-seven-day intervals, the last period being Aug. 27 and 28, 1935. The periods from September through November

though the follicular hormone continues its activity during the second phase of the cycle, the corpus luteum hormone dominates the picture and converts the endometrium into the secretory stage.* The latter is characterized by the large, convoluted, saw-toothed secreting glands, lined by simple, columnar epithelium. The stroma is composed of large pale polygonal cells. Shortly before the onset of menstruation the stroma becomes markedly edematous and hemorrhagic, and the entire endometrium assumes a cloudy, "cooked" appearance. During menstruation the functional layer of endometrium is cast off and the defect is soon repaired by the regeneration of glandular and stromal elements of the basal layer.

Should ovulation fail to occur, the follicle persists and the endometrium remains in the proliferative phase. If the action of the estradiol, secreted by the persistent follicle, is prolonged and unopposed by progesterone, the endometrium assumes a swiss-cheese pattern. It becomes thick due to an increase in the number and size of the glands, many of which are enormously dilated. The histologic characteristics of the glands and stroma are the same as in the simple proliferative endometrium. Although the cystic endometrium is frequently associated with excessive bleeding, this bleeding differs from true menstruation in that it is unaccompanied by true endometrial desquamation.

We have found five specimens of mixed endometrium in biopsies on four women with disturbed menstrual cycles.† The following study of the pathogenesis of the mixed endometrium was made in order to elucidate the nature of the underlying derangement of ovarian function.

CASE REPORTS

CASE 1.—Oligomenorrhea, mixed endometrium. M. R., aged 34, para ii, onset of menses at 14 years, periods regular every four weeks, moderate flow of six to seven days without dysmenorrhea. Following a regular six-day period (Aug. 16 to 21, 1934) there was amenorrhea for two months. This was succeeded by irregular, occasionally profuse bleeding for three months which ended on Jan. 18, 1935. Two months later profuse bleeding recurred and continued for two weeks (Mar. 14 to 28, 1935) when the patient entered the hospital.

Examination at this time revealed a uterus of normal size and an absence of adnexal pathology. An endometrial specimen on April 1, 1935 showed marked cystic hyperplasia (Fig. 1, A) but the smaller glands were in an early secretory stage (Fig. 1, B). The stroma cells had proliferative characteristics. The patient flowed moderately from April 4 to 10, 1935. This could have been a menstrual period. On April 30, 1935 another biopsy was taken and again revealed a similar mixed picture. A menstrual flow followed from May 2 to 7, 1935.

The first specimen revealed a mixed endometrium following a prolonged cycle. The same appearance was noted in the second specimen after a cycle of normal length.

CASE 2.—Oligomenorrhea, mixed endometrium. D. P., aged 31, onset of menses at 16 years, periods occurred at intervals of two to three months, moderate flow for ten days without dysmenorrhea. Following her only pregnancy in 1929, the periods

*This secretory transformation proceeds in an irregular patchy fashion so that for a short time following ovulation the same endometrial specimen may reveal some areas in the proliferative phase and others in the secretory phase. Traut and Kuder¹ have recently referred to this temporary *transitional* endometrium as "irregular ripening." We have excluded it, however, from our concept of a mixed endometrium.

†Since this paper was submitted for publication, we have obtained twelve additional specimens.

A.



B.



C.

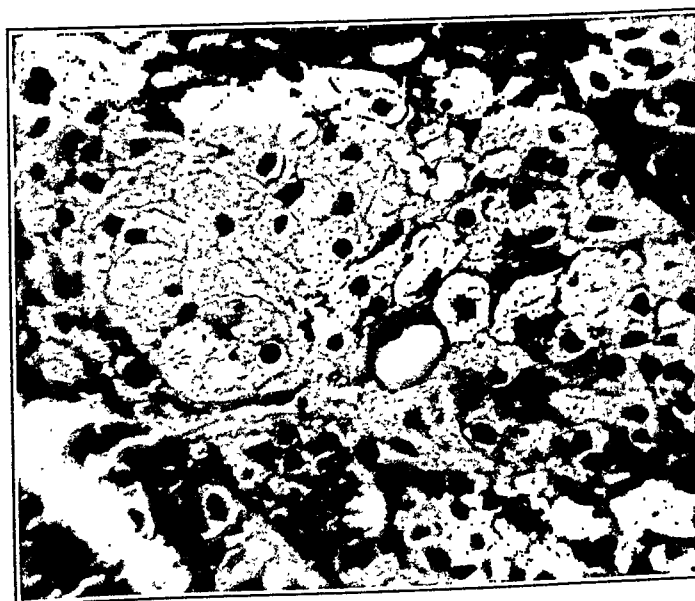


Fig. 3.—Case 4. Secondary amenorrhea with ovulatory cycle. Mixed endometrium. (A) Cystic glands, secreting glands, edematous stroma. (B) Actively secreting glands (high power). (C) Decidual-like stroma cells (high power).

were skipped. A biopsy on Nov. 16, 1935 showed an early proliferative endometrium with small nonsecreting glands and a dense stroma. Another biopsy three weeks later (Dec. 7, 1935) revealed a typical secretory endometrium. A five-day flow began on the following day. Thus, the last delayed cycle showed no mixed features. The delay though limited to the follicular phase was unaccompanied by cystic changes.

CASE 3.—Oligomenorrhea, mixed endometrium. H. C., aged 23 years, onset of menses at 15, regular every twenty-eight days, moderate five-day flow without dysmenorrhea. Last regular period Dec. 10 to 14, 1935. The next period was skipped and on Feb. 17, 1936 she began to flow moderately. The bleeding however continued until March 28, 1936 when a curettage was performed. The uterus was normal in size and consistency; both ovaries were slightly enlarged. The curettings revealed large cystic glands lined by pseudostratified epithelium and, finally, small glands lined by simple cuboidal epithelium. The latter glands gave the impression of having recently been secreting but actual secretion was not seen. The stroma cells



Fig. 2.—Case 2. Mixed endometrium. Endometrium cystic but stroma cells are large and pale resembling those of a secretory endometrium.

were large and pale, and there were many areas of pericapillary edema. The stroma was as of the secretory phase; most of the glands resembled those of the cystic endometrium. There was no evidence of gestation.

The next period occurred on Apr. 15 to 19, 1936. On May 9, 1936 prior to the expected date of the subsequent menstruation, biopsy revealed a typical secretory endometrium.

Thus in a young woman with a previously normal menstrual cycle, a delayed period was followed by prolonged bleeding and the endometrium showed a mixed picture. The normal menstrual rhythm then returned.

CASE 4.—Secondary amenorrhea, mixed endometrium. S. M., aged 35, amenorrhea of two years' duration. Menses irregular since onset at 14 years. No genital hypoplasia. Basal metabolism was minus 4 per cent. Normal urinary hormone findings, no follicle-stimulating hormone; 10 to 40 R.U. of follicular hormone per liter. Biopsy specimens obtained at intervals during a period of one and a half years showed the proliferative phase at times and the secretory picture at other times.

would prolong the secretory phase. The spontaneous occurrence of a mixed endometrium is therefore limited to ovulatory cycles in which the estrogenic hormone exerts an excessive influence during the follicular portion of the cycle. To the cystic endometrium thus produced secretory characteristics are added following ovulation.

In three of the four cases described above, the interval between periods was prolonged. This intermenstrual delay seems to be significant because of the additional time permitted the follicular hormone to exert an undue influence on the endometrium. However, a mixed endometrium may also occur in cycles of normal length. The only essential condition is that sufficient estrogenic hormone is secreted prior to ovulation to make the endometrium cystic. We have been able to produce a cystic endometrium experimentally within two weeks by administering 80,000 R.U. of progynon-B (40 mg.) during the first half of the cycle. Prolongation of the follicular phase does not necessarily result in a mixed endometrium because the hormone production in many cases of oligomenorrhea is definitely subnormal.

We next attempted to produce this mixed histologic picture experimentally. The two following methods seemed reasonable:

1. The administration of large doses of *estrogenic hormone* during the follicular portion of a normal ovulatory cycle.
2. The administration of large doses of *progesterone* during an anovulatory cycle associated with a "swiss-cheese" endometrium.

CASE 5.—*Estrogenic hormone, delayed period, mixed endometrium.* M. C., aged 27, marked lower girdle adiposity, para iv. Menses regular since onset at 13, twenty-eight day cycle, three or four days, moderate flow, without dysmenorrhea. Genital tract normal.

The patient had a regular period from Oct. 28 to 31, 1935. Two injections of progynon-B (10,000 R.U. each) were given on Nov. 2 and 9, 1935. The following period was two weeks late (Dec. 9 to 12, 1935). Biopsy on Nov. 23, 1935 revealed a proliferative endometrium. One week later (Nov. 30, 1935) the endometrium was in the early secretory phase, and the following week (Dec. 7, 1935) in a late secretory phase. The last biopsy revealed an area of large cystic glands lined by simple columnar epithelium. The stroma cells were large and there was considerable edema of the stroma. By delaying the period only the follicular phase was prolonged. This permitted the formation of cystic areas in the endometrium which, following ovulation, underwent secretory transformation.

A similar experiment was performed on the same patient using a larger amount of estrogenic hormone. The last regular period was Oct. 15 to 18, 1936. Progynon-B (20,000 R.U.) was injected on Oct. 20, 1936 and again on Oct. 27, 1936. The following period was also delayed two weeks (Nov. 27 to 30, 1936). Biopsy on Nov. 10, 1936 showed a proliferative endometrium (Fig. 4), on Nov. 17, 1936 an early secretory endometrium but, in addition, several areas with markedly dilated glands (Fig. 5). The cystic glands were lined by a nonsecreting pseudostratified epithelium while the stroma was typical of the secretory phase. On Nov. 24, 1936 a third biopsy revealed a late secretory endometrium (Fig. 6). The stroma was markedly edematous and hemorrhagic. A few glands were slightly dilated. Here again was a delayed period with a prolonged proliferative phase and cystic glands. Finally ovulation occurred and the secretory transformation proceeded at the usual

The administration of large doses of progynon-B was followed by regular scanty periods. On several of these occasions biopsy showed a secretory endometrium. The periods stopped after discontinuation of treatment on July 18, 1935. An endometrial biopsy (Fig. 3, *A*) on Oct. 1, 1935 revealed many round dilated glands lined by simple cuboidal epithelium and, in addition, normal-size actively secreting glands lined by simple columnar epithelium (Fig. 3, *B*). The stroma was markedly edematous and contained large pale decidua-like cells with well-defined outlines (Fig. 3, *C*).

This woman was thus ovulating without menstruating. On the occasion that a mixed endometrium was found, there was probably some antecedent derangement of the ovarian cycle which was reflected in the endometrium.

DISCUSSION

There are four possible ways in which a mixed endometrium might develop:

1. *Excessive production of follicular hormone during the follicular portion of the cycle.* This would result in the formation of a cystic endometrium to which secretory effects would be added following ovulation.

2. *Excessive production of follicular hormone during the luteal phase.* This probably does not occur in nature, but we tried to simulate such a condition by administering 40,000 R.U. of progynon-B (200 mg.) during the last two weeks of a normal menstrual cycle. The period occurred a few days earlier than usual. The secretory endometrium obtained by biopsy at the onset of the flow while extraordinarily thick showed no cystic changes. Perhaps there was insufficient time for cystic glands to develop or perhaps they are unable to develop once the endometrium has been influenced by the corpus luteum.

3. *Excessive production of progesterone during the follicular stage.* This appears impossible in nature because the corpus luteum does not form until the proliferative phase is complete. If progesterone were injected during the early part of the follicular phase, it would probably find the endometrium unable to respond. In the characteristic cystic endometrium, which is merely an overgrown proliferative endometrium, ovulation and luteinization characteristically fail to occur. However, when progesterone is administered in these cases, the endometrium is cast off before mixed features can develop.

4. *Excessive production of progesterone during the luteal phase.* It is questionable if this occurs at all. If it did, it would probably merely intensify the secretory effects already present.

Our experience with late menstrual (ovulatory) cycles indicates that the delay is due entirely to prolongation of the follicular phase. This is in agreement with the opinion of Campbell² that the duration of the luteal phase is limited to about fourteen days. The persistence of an actively secreting corpus luteum beyond this period must be a rarity. We have never encountered an endometrial section that suggested this condition. Possibly the premenstrual administration of progesterone

The last flow was Sept. 24 to Oct. 3, 1935. Biopsy at the onset of the flow showed a cystic endometrium. Five rabbit unit doses of progesterone (poluton-Schering) were injected on Oct. 22, 24, 26, and 29, 1935. A profuse flow followed on Oct. 28, 1935 and continued to Nov. 3, 1935. Biopsy on Nov. 2, 1935 revealed a post-menstrual type of proliferative endometrium with small straight, nonsecreting glands lined by pseudostratified epithelium. The stroma cells, however, were much larger than would be expected to accompany the glands; they were pale and resembled



Fig. 6.—Case 5. The following week. Late secretory endometrium.



Fig. 7.—Case 6. Endometrium after 45 Rb. U. of progesterone. Small glands in proliferative phase. No cystic glands present.

more the stroma cells of the premenstrual endometrium. Subsequently, after progesterone was discontinued, the cystic endometrium reappeared.

Another attempt was made six weeks later using a total of 45 rabbit units of progesterone (5 Rb. U. every other day). After the fourth injection bleeding occurred and, again, biopsy revealed a postmenstrual proliferative endometrium. The cystic endometrium under the influence of the corpus luteum hormone was apparently cast off and replaced by a new endometrium (Fig. 7). The small new glands did not show secretion probably because they had not developed sufficiently. Clauberg³ and Hamblen⁴ previously reported similar observations. The endometrium

pace. When 80,000 R.U. of progynon-B were given to this patient during the first half of the cycle, a cystic endometrium was found two weeks after the onset of the period. Subsequent weekly biopsies revealed the return to an ordinary proliferative endometrium when the injections were discontinued. Ovulation occurred during the fifth week and menstruation during the seventh week.

We then attempted to produce the mixed endometrium in another way, by the administration of large doses of progesterone to two women with persistent cystic endometrial hyperplasia.



Fig. 4.—Case 5. Experimental production of mixed endometrium. Early proliferative phase four weeks after last period. Next period delayed two weeks by 40,000 R. U. progynon-B.



Fig. 5.—Case 5. One week later. Mixed endometrium. Small glands adjoining the cystic glands in early secretory stage.

CASE 6.—Maturity bleeding, cystic endometrium, progesterone. M. P., aged 34, married twelve years, never pregnant. Onset of menses at 14 years. Periods regular the first six months only; then became totally irregular alternating between amenorrhea and profuse and prolonged bleeding. For the past ten years the bleeding has been almost constant though not always profuse. Patient has marked obesity of the trunk type. Numerous biopsies during the past four years have consistently revealed a "swiss-cheese" endometrium. Intensive therapy with pregnancy urine extract (follutein-Squibb) converted the almost continuous bleeding into a more moderate periodic flow but without appreciable change in the endometrium.

FULL-TERM ABDOMINAL PREGNANCY WITH RECOVERY OF BOTH MOTHER AND BABY

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THE following is a history of a full-term abdominal pregnancy, operated upon on Sept. 14, 1936, by the senior author (W. D. C.).

Patient M. G., white, American, 29 years of age, was admitted to the Columbus Hospital on Sept. 14, 1936, with a diagnosis of a transverse presentation, and possible dystocia due to a fibroid. Her last period was Dec. 6, 1935. Her previous history was negative except that four years ago she had a tuboovarian infection which confined her to bed for six weeks. Repeated smears at that time were negative for Neisserian infection. Two years ago a mastectomy for a Schimmelbusch disease of the left breast was done (W. D. C.).

When the patient was first seen in February, 1936, the uterus was only slightly enlarged and the patient complained of hyperemesis gravidarum. Glucose and corpus luteum intravenously cleared up her vomiting. An Aschheim-Zondek test done by Dr. Casilli was positive. Her red cell count was 3,300,000; Wassermann and Kahn tests, negative; urine, negative; hemoglobin, 50 per cent. The patient improved and had no other symptoms.

At seven months her abdomen became abnormally distended. It was transversely ovoid and at that time she was informed that she had a malpresentation. Blood pressure and urine were negative. Her initial weight was 115 pounds and on admission to the hospital it was 137½ pounds.

At full term, x-ray confirmed the diagnosis of transverse presentation. Fetal parts were easily palpable. The head was in the left iliac fossa and the extremities in the right iliac fossa and the convexity of the back toward the pelvic inlet. A mass could be palpated below and to the left of the umbilicus which on palpation would harden and then disappear. Fetal heart was plainly audible to the left and below the umbilicus (140 beats per minute).

We saw the patient in consultation on Sept. 14, 1936, and agreed that a transverse presentation in a primipara with normal pelvic measurements and a normal sized child was unusual, and that she might have a fibroid obstructing the inlet. However, we were not satisfied that this mass was a fibroid because it had a tendency to soften, and we believed it might be a part of the uterus. Rectal examination revealed a firm cervix with no dilatation of the external os and a marked fluctuation in the cul-de-sac of Douglas. No fetal parts could be palpated by rectum. Being a primipara with a transverse presentation, with a rigid cervix and a possibility of a mass, cesarean section was advised.

We attempted external version with no result. A low cervical cesarean section was planned, but on opening the abdomen, the uterus was found about the size of a three months' pregnancy. It was injected, flattened anteroposteriorly, and arising from its posterior surface and both sides was a tremendous sac with large tortuous vessels. Passing the hand upwards, it was possible to feel the placenta. An abdominal pregnancy was diagnosed. The omentum covered the sac like an umbrella, with large vessels leading from the omentum into the placenta. On each side, the amniotic sac was fused with the colon. Above the uterus was an area about three inches in diameter which appeared free of vascularity and through which an incision was made. The child was then easily delivered and it started to breathe at once. Bleeding by this time was profuse so immediately the sac cavity was packed. The question then arose as to how the placenta should be handled; to leave it in

subsequently became cystic again. The temporary shedding of endometrium induced by progesterone is thus equivalent to a curettage. Browne⁵ has also made the same observations.

CASE 7.—*Puberty bleeding, cystic endometrium, progesterone.* J. L., aged 20, onset of menses at 15 years, cycle always irregular, profuse flow of four to ten days' duration at intervals of two to six weeks. Patient bled profusely and continuously from Dec. 5, 1932 to Jan. 10, 1933. The hemoglobin was 40 per cent. Curettings revealed a "swiss-cheese" endometrium. After intensive therapy with pregnancy urine extract the bleeding stopped. Five blood transfusions were necessary to combat the anemia. Following this episode, there was no bleeding for eight months. Another period of bleeding then ensued but was quickly controlled with the same form of therapy. Subsequently there was complete amenorrhea for twenty-seven months, during which time biopsies revealed a persistence of the cystic endometrium.

Progesterone in 5 Rb. U. doses was administered every third day for five doses beginning Mar. 23, 1936. Following the second injection staining occurred and continued for one week. Biopsy on Apr. 10, 1936 revealed a proliferative endometrium. A few slightly dilated glands were seen but none were cystic. The stroma cells were small.

On May 19, 1936 the same experiment was repeated. This was followed by bleeding. Biopsy again showed endometrial glands of the usual type but the stroma cells were considerably larger than would be expected at this stage of a normal menstrual cycle. Thus the stroma alone showed the progesterone influence.

SUMMARY AND CONCLUSIONS

1. A mixed endometrium is described. It is characterized by the presence of cystic glands in association with secreting glands, or decidual-like stroma cells, or both.

2. The pathogenesis of the mixed endometrium is discussed. Its spontaneous occurrence is limited to ovulatory cycles in which there is excessive action of the estrogenic hormone during the follicular phase. The latter may or may not be delayed.

3. The mixed endometrium was experimentally produced in a woman with normal menses by prolonging and intensifying the follicular phase by means of estrogenic hormone. The attempt to produce it by the administration of progesterone during anovulatory cycles was unsuccessful due to endometrial desquamation.

4. The significance of the mixed endometrium is as follows: it demonstrates that the endometrium is an accurate indicator of the different phases of ovarian function.

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Editorial Comment

The Trend of Modern Obstetrics

THAT progress should be measured by favorable results, applies to medicine or specifically to obstetrics as it does to other activities. Recent years have witnessed remarkable changes and improvements in the conduct of pregnancy and labor. Dissatisfied with the record of fatalities attending childbearing, the profession has undertaken the task of developing corrective measures, adequately aided by other groups which have associated themselves in the task of providing adequate and satisfactory obstetric care. Public interest has stimulated the institution of numerous agencies which have discussed means and methods of making childbearing safe. The causes of the high maternal death rate of this country have been sought and evaluated.

A noteworthy contribution is that made by Dr. Frank W. Lynch at the last Clinical Congress of the American College of Surgeons in which a frank discussion was presented dealing with the relation of "radical" obstetrics to maternal mortality. As pointed out by Lynch and other competent observers, improved methods of anesthesia and operative technique and the increased opportunities for interference with labor afforded by hospitalization of obstetric patients, have developed radical tendencies entirely out of step with the ultraconservative views of former days. As Lynch so well states "the radical school feels that childbirth in the hands of nature is too crude to fit in with the ideas of modern life." Much surgery has followed but whether for good remains to be seen. Moreover we are confronted with the fact that it has had little effect in reducing maternal mortality, therefore we must question the merit of its aims notwithstanding the claims made by the defenders of radical methods, that morbidity and mortality are thus reduced. Improved public health and other facilities in developing better hygiene of pregnancy have cut down the incidence of toxemia and similar states; but shock, hemorrhage and sepsis maintain their toll of victims, and these must be ascribed to other factors.

Judgment respecting fatalities has taken on new meanings since the preventability factor was featured in the New York Academy of Medicine Report on Maternal Mortality. Lynch considers that in some centers the maternal mortality rate actually has risen because the deaths termed "preventable" are increasing faster than the nonpreventable deaths are decreasing."

and sew up the abdomen, to marsupialize it, or to remove it. It was possible to get a hand under the omentum close to the transverse colon and stomach. It was clamped and cut between clamps and on reaching the splenic flexure of the transverse colon, a line of cleavage was found, and the amniotic sac peeled quite readily from the descending colon and pelvic colon. But on the right side, part of the placenta and amniotic sac was firmly adherent to the appendix which was removed. The abdomen was sewed up tight. While being bandaged she passed from her vagina a piece of membranous tissue which proved to be true uterine cast composed of decidual cells without villi.

The patient was in shock, pulse was 160 for three days. She received three transfusions 700 c.c., 300 c.c., and 300 c.c. Continuous venoclysis of 5 per cent glucose in normal saline was given. At 5 A.M. on the second day, she developed an acute dilatation of the stomach, and with the use of a Levine tube, supplemented by the use of eserine, she rallied. Temperature remained at 103° F., and pulse at 160 for three days. On the fourth day, both temperature and pulse came down to normal. She was up on the thirteenth day after delivery and home on the seventeenth day. The child was a normal child weighing 5 pounds 14 ounces, at birth, and 6 pounds 9 ounces on discharge from the hospital.

In retrospect, the salient features in this case were: (1) Previous history of tuboovarian infection. (2) Failure of the uterus to enlarge commensurate with the date of pregnancy. (3) Sudden distention of the abdomen after seven months. (4) The abnormal presentation. (5) The presence of a mass in the lower abdomen which felt like a fibroid. (6) The boggy fluctuation of the cul-de-sac.

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In cases of hydatid moles there are two dangers. The first lies in the mole itself and consists of hemorrhage, toxic symptoms, destruction of the uterus, embolism, infection, etc. The second danger is the possibility of a malignant change resulting in a chorionepithelioma. Among the studied 11 patients with moles, 6 were between forty-one and forty-nine years of age. This is in accordance with the view that hydatid moles occur chiefly during the preclimacteric period. A very small mole may be expelled completely. Large ones have a tendency to penetrate veins and the uterine wall.

As a result of his histologic study of the 11 uteri, the author believes the following are suspicious but not definite indications of malignancy: large masses of growing epithelial elements, either in the decidua or the uterine muscle, and the duration of the viability of these cells even when there are not many present. If the body cannot destroy these cells in due time, they may lead to a chorionepithelioma. A curettement does not necessarily imply complete removal of a hydatid mole. The only certain way to determine the absence or presence of living molar tissue is by means of the Aschheim-Zondek test.

All women who have had hydatid moles should be carefully followed up. In some cases the bleeding which follows is due not to the development of a malignant condition but to degeneration and infection of retained molar products. A positive Aschheim-Zondek test indicates live chorionic tissue.

In most cases where ovarian cysts are present in cases of hydatid mole, the cysts disappear after the mole is removed. Should these cysts remain, the uterus should be investigated for tissue which was not removed.

J. P. GREENHILL.

Epidemic Diarrhea of the Newborn

FOR several years reports have been published of outbreaks of diarrhea in the newborn with a resultant case mortality rate reaching as high as 45 per cent. The disease is epidemic in character but has many mysterious features: post-mortem examinations and various laboratory tests have failed to reveal any definite information of its etiology or transmission. Various observers claim that this disease constitutes a well-defined clinical entity and deserves consideration apart from other diarrheal disturbances of infancy. Epidemics have been reported in several of our larger American cities and likewise in Europe. Within a three-year period New York had 27 outbreaks in 19 different hospitals. Chicago has had similar experiences. The problem is a serious one and until we know more about it, methods of attack necessarily must reside in preventive measures directed to the probable entrance of infection, namely the baby's nose and mouth, which means that institutional obstetric and nursing technique be developed with this end in view.

The epidemic evidently is limited to institutions and with the constantly mounting number of hospital confinements, especially in our larger cities, control measures must include not only the handling of an individual outbreak by accepted methods employed in communicable diseases, but the prevention of further outbreaks by a thorough study of the physical equipment of the particular delivery service. The obstetrician's responsibility in this problem is a very evident one. Maternity hospitals, some in name only, have expanded greatly and largely without adequate control of either staff or facilities. Nurseries in many of these are conducted on the principle of "mass collective care" without regard in certain instances to the most elementary principles of sanitation and asepsis. It is essential that health departments and other supervisory agencies develop adequate means and methods of inspection and control over lying-in hospitals and nursing homes, so that the loss of lives among the newborn from this source be checked. If the profession and the public demand hospital care for delivery, the element of danger to life must be avoided for the baby as well as the mother. Both are at a premium.

Dr. John L. Rice, Health Commissioner of New York City, has emphasized the need for sensitizing the country against this epidemic, so that more satisfactory information may be developed for combating it. If due to overcrowded nurseries or to breaks in their aseptic conduct, the measures of prevention should not be far to seek.

The responsibility for instituting reform resides, however, in the obstetrician as much as in the pediatricist, although to the latter there is delegated in many instances, the care of the newborn. If more definite cooperation is needed to obtain the desired improvement, further co-operative efforts must be developed to overcome this unfortunate epidemic disease, with its resultant high mortality rate.

Claims have been made that it is unfair to judge the matter in this fashion, because many of these deaths occurred in the hands of untrained men and the responsibility therefore cannot be ascribed to those with a radical point of view but who, as a matter of fact, are more expert. This evades the question, for we can only judge the final outcome by good average care in a country so widespread and as large as the United States. Radicalism in obstetric practice cannot be said to have compensated the outlay in means and effort which have been expanded, if we are to judge by the final results. What should be done to institute a levelling process? Lynch believes that the new school of obstetrics needs proper molding by the adequate control of men and procedures and proposes that only well-qualified operators be allowed to undertake major obstetric surgery.

Maternal mortality rates may not interest the untrained obstetrician but they are of interest to governmental agencies and may serve, rightly or wrongly, as a prominent factor in the possible introduction of a certain degree at least of Federal control of medical practice. One may differ from this thought. Education, not legislation, is the proper and the better remedy and this must be self-imposed. Organized medicine is doing its share. The American College of Surgeons has instituted a supervisory service for accredited hospitals but the loop-holes exist in our numerous independent institutions, often dominated mistakenly as maternity hospitals, which do not follow accepted standards of admission to their privileges and afford opportunities to the general practitioner who thus attempts more than he is qualified to do by training or equipment.

Fortunately, most confinements terminate normally, but we have interposed routine analgesia for pain relief, we have attempted short cuts in labor, we have developed operative terminations to delivery where these are uncalled for, we have neglected or set aside the "obstetric conscience." This appears as an arraignment which undoubtedly will be resented, but the facts based on prevalent high maternal, stillbirth, and neonatal mortality rates, call for a revision of present-day practices if we are to show any improvement.

Medical schools cannot train all of their students as expert obstetricians. They are equipped to furnish merely the ground work. Graduate education in obstetrics undoubtedly is improving, but there are not sufficient opportunities for acquiring the judgment and technical skill which is so essential for the proper conduct of labor. If, as Lynch believes, we must develop more competently staffed maternity services in general hospitals, so that a larger group can obtain adequate experience, that suggestion should be given earnest consideration. However, this will be of little avail unless we can come to some fairly definite agreement about the limitations concerned with conservatism and radicalism in obstetric procedures. In view of the prevailing differences of opinion this will not be a simple task but, like many other problems of medical practice, it can best be solved by the profession itself and constitutes a challenge which must be met. American obstetrics has reached a high estate; it can well undertake to solve its problems.

TABLE I. BIRTH AND MATERNAL DEATH STATISTICS, ACCORDING TO RACE

	LIVE BIRTHS COUNTIES MARYLAND, 1934	DEATHS ABORTION	DEATHS OTHER	TOTAL DEATHS
White	10,951	80	241	321
Black	2,913	14	112	126
White	78.99%	85.11%	68.27%	71.81%
Black	21.01	14.89	31.73	28.19

The same racial disparity is illustrated in Table I. Deaths listed as abortion do not include ectopic pregnancy, therapeutic abortion, or undelivered women dying prior to the seventh month of pregnancy. The contrast between these deaths and those occurring in late pregnancy, labor, and the puerperium is significant as is evidenced by the following ratios (approximate) found for the colored race: total births 1 in 5; deaths abortion, 1 in 7; deaths other, 1 in 3. It is believed that the column "deaths other" reveals the true racial difference more accurately than does "total deaths" since the majority of abortion deaths were due to sepsis following criminal procedures, and it is uncommon for the colored woman to employ active means towards the premature termination of a pregnancy.

TABLE IIA. AGE OF WOMEN IN SERIES AT TIME OF DEATH SUBDIVIDED BY RACE AND PARITY (OMITTING UNKNOWN)

AGE	WHITE				BLACK				TOTAL WHITE		TOTAL BLACK	
	PRIMIPARAS		MULTIPARAS		PRIMIPARAS		MULTIPARAS		NO.	%	NO.	%
	NO.	%	NO.	%	NO.	%	NO.	%				
-14	4	3.74	0	0.00	3	6.25	0	0.00	4	1.25	3	2.38
15-19	41	38.32	8	5.13	28	58.33	5	8.62	50	15.58	35	27.78
20-24	30	28.04	15	9.62	11	22.92	10	17.24	58	18.07	24	19.05
25-29	15	14.02	24	15.38	1	2.08	10	17.24	57	17.76	18	14.29
30-34	10	9.35	25	16.03	2	4.17	11	18.97	48	14.95	18	14.29
35-39	3	2.80	50	32.05	2	4.17	11	18.97	59	18.38	15	11.90
40-44	4	3.74	32	20.51	1	2.08	7	12.07	43	13.40	9	7.14
45-	0	0.00	2	1.28	0	0.00	4	6.90	2	0.62	4	3.17
Total	107	100.01	156	100.00	48	100.00	58	100.01	321	100.01	126	100.01

TABLE IIB. MEAN AGE OF WOMEN ACCORDING TO BIRTHS (U. S., 1934) AND DEATHS (MARYLAND, 1930-1936)

	BIRTHS		MATERNAL DEATHS	
	YEARS	MONTHS	YEARS	MONTHS
White, primiparas	23	3	23	0
multiparas	29	6	33	10
Black, primiparas	20	4	20	6
multiparas	27	11	31	10
Total, white	27	6	29	7
black	25	10	27	0

Age.—It is generally stated that early childbearing is to be preferred from an obstetric standpoint and statistical analyses have appeared indicating that the course of pregnancy, labor, and the puerperium in the "young primipara" (aged 16 or less) is accompanied by a minimum of complications and a favorable maternal and fetal mortality. Conversely, elderly primiparity (aged 35 or more) is usually believed to be attended by increasing hazards to mother and child, although little has been said concerning the effect of advancing age upon the multiparous woman.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

A SURVEY OF 447 MATERNAL DEATHS OCCURRING IN THE COUNTIES OF MARYLAND DURING THE YEARS 1930-1936 (INCLUSIVE)

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DURING recent years the high maternal mortality rates throughout the United States have received increasing attention from physicians, health authorities, and lay press, alike. A number of statistical analyses dealing with this subject have appeared, most of them recounting the record of maternity hospitals or the experience of large cities. In 1933 the Children's Bureau of the Department of Labor published an exhaustive report on "Maternal Mortality in Fifteen States" for the years 1927 and 1928. Comprehensive analyses of results in smaller communities and rural areas have been few. Knox, in 1931, wrote a brief analysis of 241 maternal deaths occurring in the counties of Maryland, exclusive of the city of Baltimore, during the years 1927 to 1929, inclusive. This survey was made possible by data accumulated through personal interviews with the physician or midwife concerned in each instance. Since the above date, the practice of making surveys on all maternal deaths has continued and over the seven-year period ending Dec. 31, 1936, an additional 447 cases have been recorded. The following comprises an analysis of the various items of information obtained from the survey blanks as transmitted to the State Department of Health.

It should be emphasized in advance that these 447 maternal deaths occurred in the counties and do not include a number of rural patients transported to and dying in the hospitals of Baltimore. Maryland, exclusive of Baltimore, is predominantly rural, and there are only four other cities in the state with a population in excess of 10,000. The topography of the state varies from low-lying areas bordering on the Chesapeake Bay, to rich farm lands, to mountainous mining districts. The occupation of the inhabitants varies accordingly and the racial distribution is such that in one county the number of colored births is in excess of the white, while in another not a single one of the former is recorded. In other words, it is felt that the childbearing population of the state affords a representative cross section of the country and that conclusions drawn from this study may be applied to other sections.

Race.—Investigators throughout the United States have generally reported a higher maternal mortality rate in colored than in white women. Over an eleven-year period ending in 1935, the average death rate from puerperal causes in the counties of Maryland was 4.06 per 1,000 live births (white) as contrasted with 6.84 (black).

by an increased hazard to the mother as is evidenced by these comparative percentages of total births and maternal deaths: white primiparas 27.03 and 42.06; white multiparas 3.34 and 5.13; black primiparas 56.66 and 64.68; and black multiparas

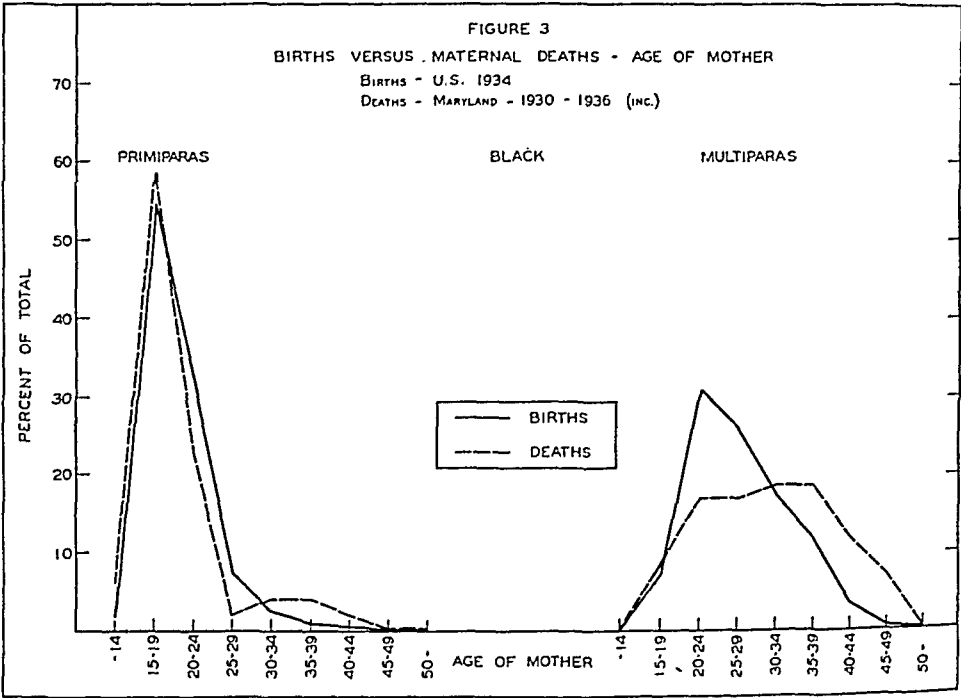


Fig. 3.

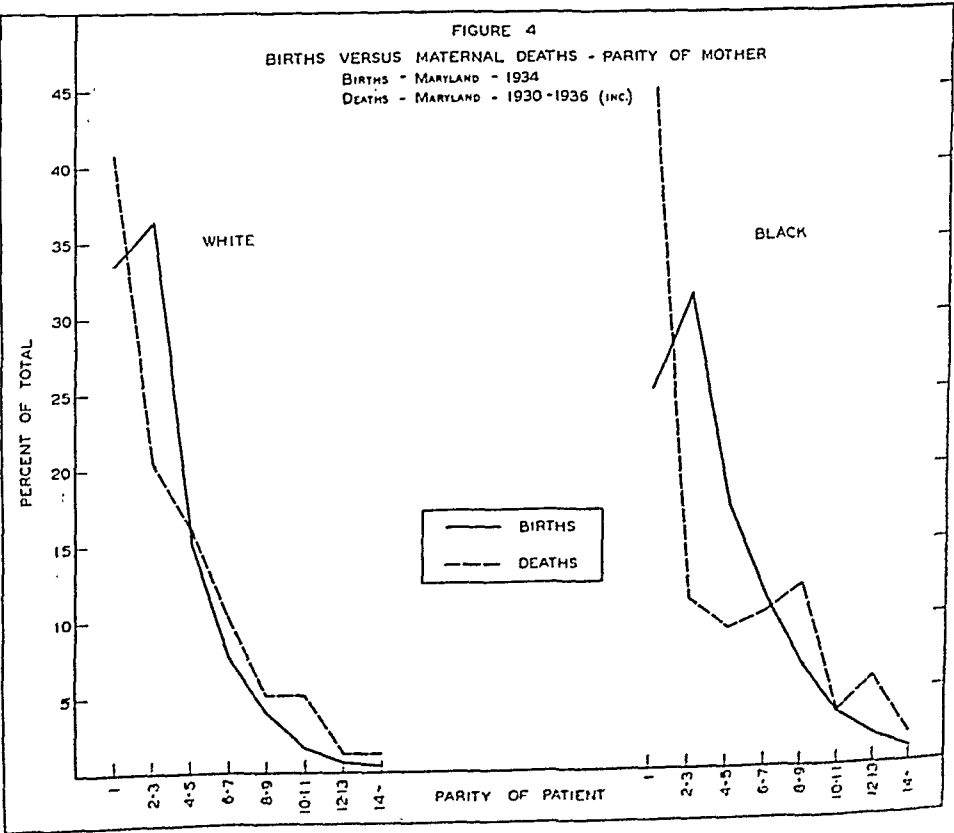


Fig. 4.

Tables II A and II B and Figs. 1 to 3 indicate the frequency distribution of the women in this series according to age at the time of death, with subdivisions for race and parity. Furthermore, a contrast is offered between this item and the age of moth-

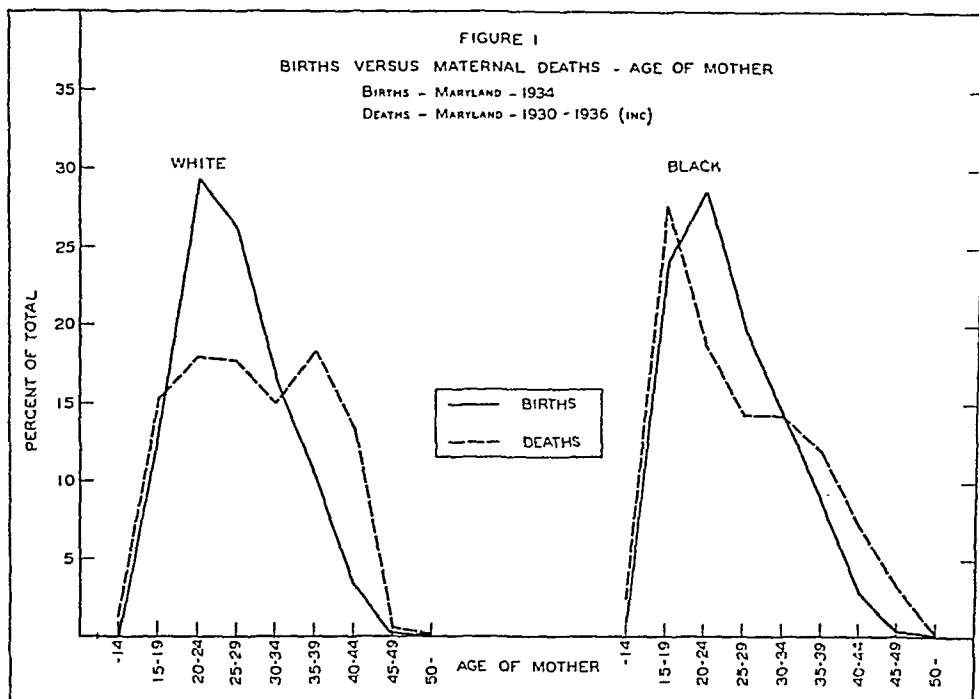


Fig. 1.

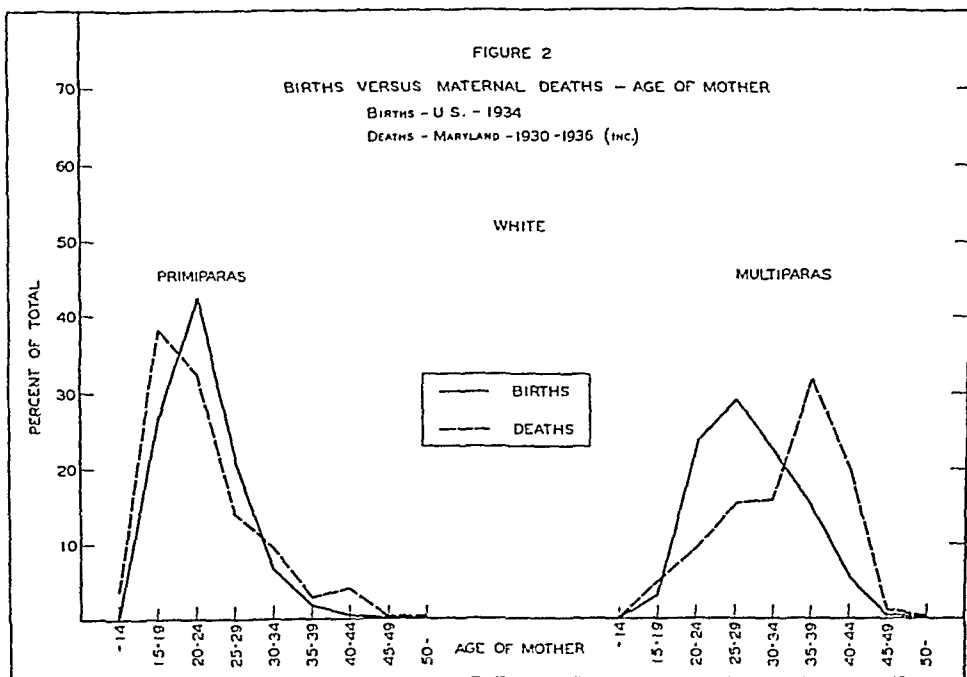


Fig. 2.

ers at the time of primiparous or multiparous births for the United States Registration Area in 1934, since a comparison between the percentage of total births versus deaths for any age group should afford an indication of the risk involved. Our experience indicates that childbirth occurring before the age of twenty is accompanied

Social Status.—The social status of the 447 women in the series is shown in Table IV. The high incidence, 25 per cent white and 28.57 per cent black, of illegitimate pregnancies in patients dying after abortion was to be expected. Excluding abortions, and due probably to inadequate obstetric care, the percentage of unmarried mothers in the series of maternal deaths was 6.64 and 33.14 for whites and blacks, respectively. A comparison is offered by the recording as illegitimate of 2.63 per cent of total births white and 23.81 per cent black in 1934 for the State of Maryland.

Prenatal Care.—It is axiomatic that adequate maternity care must include not only skilled attention at the time of delivery but also careful supervision throughout the entire pregnancy. Our figures indicate that two-thirds of women dying of puerperal causes in the counties of Maryland had never sought medical aid prior to the onset of labor or the fatal illness and that only one out of ten had had adequate prenatal care. Some difficulty was experienced in assaying the adequacy or inadequacy of prenatal supervision from the information available. It was arbitrarily determined to classify as "good" the prenatal care of those patients who had sought advice before the seventh month of pregnancy, had been seen at least twice before labor by the physician, and whose examination had included a general physical check-up, pelvic mensuration, blood pressure determination, and urinalysis. The blood Wassermann test was not included because it had been done so rarely. In a number of instances the woman was examined relatively early in pregnancy but was not seen again until delivery; the care in such cases was classified as "inadequate." Table V gives the data available on prenatal care and omits all pregnancies terminating within the first four months. It will be noted that antepartum supervision was received much more frequently by the white than the colored women in the series and that this supervision was adequate in 15.49 per cent of the former group as compared with 0.93 per cent of the latter. Furthermore, a total of 76 white and 12 colored women sought medical advice at or before the seventh month of pregnancy yet good care was experienced by only 35 of the former and one of the latter group. Table V also shows that of those women seeking prenatal care almost all had the urine examined for albumin and in the vast majority of instances the blood pressure was determined. However, in only slightly more than half, 55.56 per cent, was any attempt at pelvic mensuration made and usually this examination did not include the determination of the diagonal conjugate nor was the intertuberos diameter estimated. Finally, the Wassermann reaction was obtained only 20 times, 6.01 per cent of the patients in the series. These figures clearly indicate that two of the major weapons of modern obstetrics, namely the diagnosis of pre-existing abnormalities and the early recognition of obstetric complications, were rarely employed in this series of 447 maternal deaths. It should be emphasized that this statement must not be considered as criticism of the attendant physician for re-

TABLE V. PRENATAL CARE OF WOMEN IN SERIES (OMITTING ABORTIONS)

	NUMBER		PER CENT OF TOTAL		PER CENT TOTAL	PER CENT OF PRENATAL PTS.	
	WHITE	BLACK	WHITE	BLACK		WHITE	BLACK
Good	35	1	15.49	0.93	10.81		
Inadequate	57	17	25.22	15.89	22.22		
None or unknown	134	89	59.29	83.18	66.97		
Month First Seen							
-5	55	3	24.34	2.80	17.42	59.78	16.67
6-7	21	9	9.29	8.41	9.01	22.83	50.00
8-	12	6	5.31	5.61	5.41	13.04	33.33
Unknown	4	0	1.77	0.00	1.20	4.35	0.00
Pelvis measured	47	13	20.80	12.15	18.02	51.09	72.22
Urine examined	91	16	40.27	14.95	32.13	98.91	88.89
Blood pressure determined	85	16	37.61	14.95	30.33	92.39	88.89
Wassermann done	14	6	6.19	5.61	6.01	15.22	33.33

8.12 and 8.62, respectively. Calculated on a similar basis, the age group 20 to 34 inclusive may be considered the safest, our figures indicating a low percentage of total deaths as contrasted to births. As the end of the childbearing period nears, pregnancy is again accompanied by increased danger, particularly to the multipara as is indicated by the following percentages of births and deaths, respectively: white multiparas 20.83 and 53.84; and black multiparas 16.16 and 37.94. The above findings are further emphasized by a comparison of total births and deaths according to mean age as is shown in Table IIB. The mean age at time of death of the white multiparas in the series was four years and four months in excess of the figure derived for average age at time of delivery; while for colored multiparas a similar increase of three years eleven months was found. In other words, our experience indicates that the practice of dismissing the multiparas, aged thirty-five or more, with the term "normal" is a dangerous one, and it is in this group of women that a great many of the avoidable maternal deaths occur.

Parity.—The distribution according to parity of the women in the series is shown in Table III, while Fig. 4 affords the same contrast between total deaths and births as has been used in the discussion of effect of age. This figure indicates the expected increased hazards of primiparity, which are disproportionately high in the black as contrasted with the white woman. In the white race the second and third baby seem by far the safest to the mother and when the group para iv and v is reached, the percentage of total deaths exceeds that of births, and this discrepancy continues throughout the higher multiparous brackets, so that the incidence of total births,

TABLE III. DISTRIBUTION OF MATERNAL DEATHS ACCORDING TO PARITY
(OMITTING UNKNOWN)

PARITY	NUMBER		PER CENT	
	WHITE	BLACK	WHITE	BLACK
i	107	48	40.68	45.28
ii-iii	54	12	20.54	11.32
iv-v	42	10	15.97	9.43
vi-vii	26	11	9.88	10.38
viii-ix	14	13	5.32	12.26
x-xi	14	4	5.32	3.77
xii-xiii	3	6	1.14	5.66
xiv	3	2	1.14	1.89
Total	263	106	99.99	99.99

para iv and over, is 29.97, while the comparative figure for total deaths is 38.77 per cent. In colored women the incidence of deaths does not exceed that of births until the bracket para viii and over is reached and the contrasting figures here are 23.58 and 13.83 per cent, respectively. The reasons for this observed racial difference are not clear and may well be a sampling error alone. We believe, however, that these figures serve to emphasize once more the fact that the "grande multipara" is not a satisfactory obstetric subject, runs an increased chance of such major complications as placenta previa, rupture of the uterus, premature separation, transverse presentation, etc., and should be cared for accordingly.

TABLE IV. DISTRIBUTION OF MATERNAL DEATHS ACCORDING TO SOCIAL STATUS

	ABORTIONS		NUMBER				PER CENT					
			TOTAL WITHOUT ABORTIONS		TOTAL		TOTAL WITHOUT ABORTIONS		ABORTIONS		TOTAL	
	WHITE	BLACK	WHITE	BLACK	WHITE	BLACK	WHITE	BLACK	WHITE	BLACK	WHITE	BLACK
Married	60	10	222	74	282	84	75.00	71.43	92.12	66.07	87.85	66.67
Single	19	3	16	37	35	40	23.75	21.43	6.64	33.04	10.90	31.75
Widowed	0	1	2	1	2	2	0.00	7.14	0.83	0.89	0.62	1.59
Divorced	1	0	1	0	2	0	1.25	0.00	0.41	0.00	0.62	0.00
Total	80	14	241	112	321	126						

existing social conditions, the prevention of such deaths seems impossible. In only slightly more than half of the total cases, 52.07 per cent, had the pregnancy reached term.

Type of Delivery.—Table IX indicates the outcome to the pregnancy in the deaths under consideration. Eleven women died as the result of ruptured ectopic pregnancy, the diagnosis being confirmed at operation in 6 instances. Two deaths followed therapeutic abortion, the indication for the operative termination of pregnancy being myomata uteri and chronic nephritis, with death resulting from surgical shock following hysterectomy, and post-partum hemorrhage after curettage, respectively. Other postabortal deaths totaled 94. Almost 10 per cent of the deaths occurred before delivery, 7 being in the previable stage of pregnancy. The type of delivery (viable) was unknown in 19 instances. There remain 279 women delivered of viable fetuses, 205 of which had reached approximate maturity. Birth was spontaneous in only a little more than half of these, 57.71 per cent, with operative procedures as detailed in Table IX being employed in the remainder. Delivery by version was noted more frequently than forceps, the indication for this operation in the majority of instances being placenta previa or eclampsia. Attention is directed to the fact that 49 women died following delivery by cesarean section, 17.56 per cent of total viable births. The indication for the operation could not be ascertained from the survey blanks in 22 instances but in 22 of the remaining 27 it was *eclampsia*! The causes of death in the 49 section cases were eclampsia 21, puerperal sepsis 11, intestinal obstruction 3, and operative shock 2, with the operation itself apparently not a causative factor in the other 12.

TABLE IX. TYPE OF DELIVERY WITH REFERENCE TO DURATION OF PREGNANCY

Ectopic pregnancy			11	
Laparotomy	6			
Died without operation	5			
Therapeutic abortion			2	
Hysterectomy	1			
Dilatation and curettage	1			
Other abortions			94	
Died undelivered			42	
Type of delivery unknown			19	
Delivery at or near term			279	
	NO.	PER CENT	NO.	TERM ONLY PER CENT
Spontaneous	161	57.71	123	60.00
Forceps	27	9.68	17	8.29
Version	32	11.47	18	8.78
Breech extraction	8	2.87	6	2.93
Craniotomy	2	0.72	2	0.98
Cesarean section	49	17.56	39	19.02

Attendant at Time of Delivery.—Table X shows that for viable births delivery was effected by a physician in 9 cases out of 10. In a number of instances, however, care by a midwife was planned and the doctor summoned only because of some obstetric complication.

TABLE X. ATTENDANT AT TIME OF DELIVERY (VIALE BIRTHS ONLY)

	NO.	PER CENT
Delivered by:		
Doctor	267	89.60
Midwife	21	7.05
Neighbor	1	0.34
No attendant	6	2.01
Unknown	3	1.01

peatedly the statement appears on the survey "was not called to see this patient until shortly before her death." It is impossible to state how many of these deaths might have been avoided had the woman sought advice during the antenatal period, but an analysis of the records leads one to believe that adequate supervision at this time might have altered the end result in a substantial number of instances.

Place of Delivery.—Table VI indicates the place of delivery, or of death in those cases dying undelivered, of the cases under analysis, abortion deaths being omitted. Home and hospital deliveries seem to be about equal, but it is our belief that the information if complete would indicate a preponderance in favor of the home since in a number of cases home delivery was planned and admission to the hospital sought later because of the diagnosis of some obstetric complication.

TABLE VI. PLACE OF DELIVERY, OR DEATH, IF DIED UNDELIVERED
(OMITTING ABORTIONS AND UNKNOWN)

	NO.	PER CENT
Home	156	46.29
Undelivered, died at home	16	4.75
Hospital	139	41.25
Undelivered, died in hospital	25	7.42
Undelivered, died on way to hospital	1	0.30
Total	337	

Place of Death.—Information as to place of death is given in Table VII which indicates that approximately one-third of the total deaths occurred at home although 45 women who had been delivered of viable children were transferred to hospitals at some time, usually late, in the course of the fatal illness.

TABLE VII. PLACE OF DEATH

	NO.	PER CENT
Delivered home, died hospital	45	10.07
Delivered hospital, died hospital	136	30.43
Died undelivered, hospital	25	5.59
Abortion, died hospital	83	18.57
Delivery unknown, died hospital	3	0.67
Delivered hospital, died home	3	0.67
Delivered home, died home	111	24.83
Died undelivered, home	16	3.58
Abortion, died home	24	5.37
Undelivered, died on way to hospital	1	0.22

Duration of Pregnancy.—Analysis of the case records from the standpoint of duration of pregnancy revealed two points worthy of mention. A fourth of the total deaths followed abortion or occurred before delivery during the previable stage of the pregnancy. It will be shown subsequently that in the great majority of these cases the cause of death was postabortal sepsis, usually following criminal procedures. This is considered a large figure and attains added importance since, under

TABLE VIII. DURATION OF PREGNANCY AT TIME OF DELIVERY OR DEATH

	NO.	PER CENT	PER CENT WITHOUT UNKNOWN
Term	214	47.87	52.07
Premature	83	18.57	20.19
Abortion	114	25.50	27.74
Unknown, not abortion	36	8.05	

and black women and has a much lower incidence in Maryland than for the country as a whole. However, abortion with sepsis results fatally almost two and a half times as often in white as contrasted with colored patients, and the incidence here is definitely higher than for the total registration area. It is believed that the great majority of deaths listed under this latter heading are the results of criminal procedures. If this be accepted, the racial discrepancy is easily explained, since it is rare for the pregnant negress to employ active measures to terminate gestation. However, the finding of a higher incidence of abortion deaths in this, a series of rural women, as contrasted with the entire country is a disturbing and serious matter. Deaths following ectopic pregnancy occurred about equally in the two races and the incidence was about that for the registration area. Of the total colored deaths, 9.92 per cent were ascribed to placenta previa and other hemorrhage, while for white women the higher rate of 14.10 per cent was found. The only suggestive cause for this difference was the much greater number of operative procedures employed to effect delivery in the white women, whereas most of the colored were allowed to deliver spontaneously. Hemorrhage deaths occurred somewhat more frequently in this series than for the entire country. Puerperal sepsis (omitting postabortal infection) was listed twice as often in the colored as in the white column, despite a higher operative incidence for the latter group. This affords

TABLE XIII. APPARENT CAUSE OF DEATH FROM INFORMATION ON SURVEY BLANKS AND DISREGARDING DEATH CERTIFICATE

		%
I. Infection:		143 = 31.99
Puerperal sepsis	64	
Postabortal sepsis	77	
Intrapartum septicemia	1	
Septicemia, operation, ruptured ectopic	1	
II. Toxemia:		123 = 27.52
Eclampsia	94	
Chronic nephritis	25	
Toxemic vomiting	3	
Acute yellow atrophy	1	
III. Hemorrhage:		74 = 16.55
Post-partum hemorrhage	21	
Premature separation of placenta	8	
Placenta previa	25	
Ruptured ectopic	9	
Ruptured uterus	3	
Hemorrhage with abortion	7	
Inversion of uterus	1	
IV. Other Obstetric Complications:		53 = 11.86
Embolus	26	
Shock, delivery	18	
Intestinal obstruction after C.S.	3	
Anesthetic death	2	
Acute poisoning, attempt at abortion	2	
Fernicious anemia of pregnancy	1	
Paralytic ileus, post partum	1	
V. Nonobstetric Complications:		32 = 7.16
Chronic valvular heart disease	8	
Pneumonia	15	
Influenza	2	
Pyelitis	2	
Acute mania	2	
Status epilepticus	1	
Perinephritic abscess	1	
Peritonitis, cause unknown, undelivered	1	
VI. Unknown		22 = 4.92

Outcome to Child.—From Table XI it will be seen that, including abortions in order to ascertain the result of total pregnancies, only 43 per cent of the cases under consideration terminated in the birth of a living child. Considering only viable births a stillborn rate of approximately 1 out of 3 was obtained.

TABLE XI. OUTCOME TO CHILD

	NO.	PER CENT	PER CENT
Abortion	107	23.16	
Undelivered	42	9.09	
Stillborn	109	23.59	34.28
Alive	199	43.07	65.72
Unknown	5	1.08	

Cause of Death.—The discussion as to cause of death of the patients in the series will be given under the following two headings: (1) The cause as given on the death certificate and classified according to the international list of causes of death. This is done in order to contrast the results found with those of the United States Registration Area both total and rural. (2) A more complete listing of individual causes than is usually made in statistical analyses from maternity hospitals.

Making use of the International Classification and contrasting our experience with that for the country as a whole, several interesting points become apparent, as illustrated in Table XII. Abortion without sepsis occurs about equally in the white

TABLE XII. CAUSE OF DEATH ACCORDING TO INTERNATIONAL CLASSIFICATION INCLUDING A COMPARISON WITH THE UNITED STATES REGISTRATION AREA

(Omitting 9 White and 5 Colored Women Dying of Pneumonia)

	MARYLAND			U.S.	
	W.	C.	TOTAL	U.S.	RURAL
Abortion with sepsis	67	10	77	2037	480
Abortion without sepsis	6	2	8	640	272
Ectopic with sepsis	1	0	1	121	20
Ectopic without sepsis	6	3	9	489	93
Other accidents of pregnancy	1	0	1	88	32
Placenta previa	20	5	25	411	141
Other hemorrhage	24	7	31	928	371
Puerperal sepsis	40	30	70	2719	901
Puerperal tetanus	0	0	0	10	2
Albuminuria and eclampsia	89	47	136	2520	1110
Other toxemias	5	1	6	535	131
Phlegmasia, embolus, sudden death	27	4	31	592	234
Other accidents of childbirth	25	11	36	1750	650
Other conditions of puerperal state	1	1	2	45	11
	312	121	433	12885	4448

	MARYLAND			U.S.	
	W. %	C. %	TOTAL %	U.S. %	RURAL %
Abortion with sepsis	21.47	8.26	17.78	15.81	10.79
Abortion without sepsis	1.92	1.65	1.85	4.97	6.12
Ectopic with sepsis	0.32	0.00	0.23	0.94	0.45
Ectopic without sepsis	1.92	2.48	2.08	3.80	2.09
Other accidents of pregnancy	0.32	0.00	0.23	0.68	0.72
Placenta previa	6.41	4.13	5.77	3.19	3.17
Other hemorrhage	7.69	5.79	7.16	7.20	8.34
Puerperal sepsis	12.82	24.79	16.17	21.10	20.26
Puerperal tetanus	0.00	0.00	0.00	0.08	0.04
Albuminuria and eclampsia	28.53	38.84	31.41	19.56	24.96
Other toxemias	1.60	0.83	1.39	4.15	2.95
Phlegmasia, embolus, sudden death	8.65	3.31	7.16	4.59	5.26
Other accidents of childbirth	8.01	9.09	8.31	13.58	14.61
Other conditions of puerperal state	0.32	0.83	0.46	0.35	0.25

In other instances the physician or midwife could have been implicated by an error in judgment or technique. In this regard certain statistics found in a report on "Maternal Mortality in New York City" published in 1933 are of interest. Following an exhaustive survey of 2,041 maternal deaths it was concluded that 1,343 or 65.8 per cent must be classed as preventable and that the responsibility lay with the physician in 61.1 per cent of the latter, the patient in 36.7 per cent, and the midwife in 2.2 per cent. To what extent the experience of urban New York may be comparable to rural Maryland is difficult to estimate. It is, however, our opinion that approximately two-thirds of the 447 maternal deaths which we have analyzed were strictly preventable, that in many instances the patient herself was responsible through failure to seek and obtain prenatal care, while frequently the community was to blame because of the absence of local facilities for such care. No adequate solution to this problem has ever been presented but it is believed that adequate dissemination of contraceptive material and advice throughout the rural communities might accomplish something. However, it must be admitted that in many instances contraception, in view of present methods and the low intelligence standard of those most needing such advice, would at best serve only to delay the inevitable pregnancy. Deaths from abortion without sepsis were in the main due to bleeding. Fatal hemorrhage with abortion is not ordinarily fulminant but a protracted process enduring over a period of days. In several of our cases it seems evident that had medical advice been sought before the patient was almost exsanguinated the fatal outcome might have been avoided. Since in many rural areas prompt medical attention is not always available and hospitalization often entails many miles of transportation, deaths from *ectopic gestation* are rarely avoidable. *Placenta previa* and *other hemorrhage* accounted for approximately one-eighth of the total deaths in this series. In New York City it was stated that 76.1 per cent of such deaths were preventable and that in four-fifths of these the physician or midwife was at fault. This high degree of preventability undoubtedly exists in urban areas but in isolated communities without adequately equipped hospitals the majority are probably unavoidable. The counties of Maryland compare favorably with the rural United States in deaths due to *puerperal sepsis*. Here the untrained and slovenly midwife is often at fault, although it must be admitted that many births occur in huts so primitive and filthy as to render clean obstetrics impossible. It is believed that unsatisfactory home conditions afford as urgent an indication for hospital delivery as do the major obstetric complications. However, beds for the "normal multipara" are usually not available and in many communities can be had only by the paying patient. Current tendencies toward operative obstetrics undoubtedly account for many sepsis deaths but this is true far oftener in urban than in rural communities. Almost a third of the deaths here reported were due to *albuminuria*, *eclampsia*, and *other toxemias*, and it is in this group that the greatest number of preventable deaths occur, with the patient herself usually at fault. Adequate prenatal care would probably have prevented the toxemia from becoming severe enough to endanger life in three cases out of four. Even in New York City it was felt that the responsibility lay with the patient in 69.0 per cent of the toxemic deaths. Deaths from *phlegmasia*, *embolus*, and *sudden death* are rarely avoidable in view of present medical knowledge.

further evidence of an interesting and not understood racial difference repeatedly found by investigators. The total incidence of sepsis for the series is well under that for the Registration Area. Attention is called to the finding of a higher rate of postabortal sepsis than of infection following delivery of a viable child. The toxemias of pregnancy accounted for 30.13 per cent of the white deaths and 49.67 per cent of the black. It is believed that the racial difference is probably in terms of prenatal care which, as has been seen, was utilized more frequently by the white patient. The incidence of toxemic deaths was significantly higher in this series than in the entire country. To recapitulate, deaths from sepsis and toxemia occurred more frequently in the black than in the white women of the series, whereas the reverse was found for postabortal sepsis and hemorrhage. Also, in comparison with the United States Registration Area (rural) the counties of Maryland showed a favorable balance in deaths from puerperal sepsis but an unfavorable one for abortion and toxemia.

Analyzing the survey blanks carefully and listing individually the causes of death, it was found that infection, toxemia, and hemorrhage, in order of frequency as listed, accounted for 76.06 per cent of the total. It has been frequently stated that in the United States 40 per cent of all maternal deaths are due to infection. The figure of 31.99 per cent adduced here compares favorably with this. Toxemia follows closely upon infection as a cause of death with eclampsia accounting for the greatest number under this category. It seems likely that the figure of 94 fatalities ascribed to eclampsia is too low, and we believe that more careful diagnosis would have resulted in some of the 25 listed as chronic nephritis being placed in the former category. Those cases listed under hemorrhage seem to call for no particular comment at this time. In 22 instances information obtained from survey was too incomplete to permit an independent diagnosis being made.

DISCUSSION

A statistical analysis has been presented of 447 maternal deaths occurring in the counties of Maryland, exclusive of Baltimore City, during the years 1930 to 1936, inclusive. Comment upon the findings has been made with the summary of each individual item. Further discussion may well be limited to two points: A comparison of the experience here listed with that obtaining elsewhere; and an attempt to evaluate means of avoiding those which in the light of present medical knowledge must be listed as "preventable."

The maternal death rate for the entire state of Maryland in 1934 (the last year in which complete comparative figures were available at the time of writing), was 5.2 per 1,000 live births, and for the counties 4.2, while for the United States Registration Area, it was 5.9. Only 11 states reported a lower figure and in 3 others an identical one was found. The results in Maryland become even more favorable when it is noted that those states reporting a lower mortality rate have a much smaller colored population, and as has been stated, puerperal deaths in white women in Maryland counties over a period of eleven years was only 4.06 per 1,000 live births. It is obvious, however, that even this figure is far too high and by no means represents an approach to a minimum of what might be termed "unavoidable deaths."

The information obtained from survey was in many instances too meager to furnish a definite statement as to whether or not the death might be considered avoidable, or the responsibility placed on the patient, physician, or midwife. In many cases it seemed that the patient herself was definitely responsible, either because of failure to obtain suitable medical care or through lack of cooperation with her doctor.

paring her home for delivery. It is our belief that a prenatal program of this kind, available to everyone, will materially contribute in lowering the present high maternal mortality.

2. In rural communities, and particularly in those having a large colored population, adequately trained nurse-midwives constitute at least a temporary solution to the problem of proper care during labor and the early puerperium. In two of the counties of Maryland such nurses have been supplied by the Health Department. Their duties are various. In the first place they may give instruction to the local midwives, improving their methods and technique and attending deliveries in an effort to better standards. In physicians' cases they are with the patient (who would otherwise be unattended) during labor; they detect and report any abnormality, call the physician at the appropriate time and render him skilled aid during delivery itself. If delivery occurs before the physician's arrival, the nurses are competent to attend in the emergency. They are also of value in aiding the puerperal woman and in instructing her in the care of her newborn infant. Such a program not only contributes to the care of the indigent parturient but also is of benefit to the physician since much less of his time is required for the maternity case. The nurse-midwife becomes even more important when it is realized that in some rural sections physicians are not available or if so, decline to take obstetric cases. The midwife becomes the only solution to the maternity problem, and the role of trained nurse-midwife still more important.

3. Adequate hospital beds should be provided for the indigent obstetric patient who presents any abnormality or whose home is such that decent technique becomes impossible. Certain counties have no hospitals, others do not care for nonpaying patients, and distances are often such that transportation to the public wards of a city hospital is inadvisable. Furthermore, it would seem that local funds are as properly applicable to defray hospital expenses of eclampsia or placenta previa as of typhoid fever or pneumonia.

4. "Refresher" lectures and round table discussions of the modern approach to clinical obstetric problems would seem as important to the rural practitioner as to the one residing in a university city. Such discussions should be held at meetings of the county groups under the auspices of the state medical society.

Winter, E. W.: *What Is the Mechanism of Breast Secretion?* Wien. Klin. Wchnschr. 49: 654, 1936.

In experimental animals (rabbit, rat, and guinea pig) the breast secretion is due to a complex network of various substances. It is linked up with the ovarian and corpus luteum hormones which give rise to a lactation hormone probably through the anterior pituitary gland which in turn stimulates the breast glands and lactation follows. In the human being, the mechanism appears to be as follows: The cause of the onset of breast secretory function is due to a change in the concentration between ovarian and anterior pituitary hormones with the probable intermediation of the vegetative nervous system so that the anterior pituitary outweighs the ovarian secretion. In certain cases of tumors of the pituitary with definite anatomic changes associated with definite cell groups, breast secretory function has been observed. These observations seem to place the ultimate cause on a definite type of cell.

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It must be said, however, that *other accidents of childbirth* are largely preventable and must ascribed to errors of technique or judgment on the part of physician or midwife. Major operative procedures are too frequently attempted without proper indication, in an unfavorable environment, and on patients unable to withstand surgical trauma. Generally speaking the best results will coincide with the fewest operative deliveries.

In view of what has been said it is believed that the following recommendations offer a practical method for the reduction of rural maternal mortality.

1. The advantages of prenatal care should be made known to every pregnant woman and adequate care should be immediately available to her. Despite an earnest attempt on the part of the medical profession and considerable recent publicity by the lay press the average rural woman does not seek examination and advice in the antenatal period unless symptoms develop which are sufficiently disquieting to persuade her to do so. The relatively rare so-called "full pay" patient is an exception to this and in most rural areas of our experience seems to be seeking and obtaining relatively adequate prenatal supervision. The majority of white women of a lower financial scale call the physician only after labor supervenes. The remainder of this group and most of the colored women plan to be delivered by midwives who themselves are unable to offer intelligent advice. A slowly but steadily increasing percentage of pregnant women in the counties of Maryland have been obtaining prenatal care in recent years as the result of efforts on the part of three separate groups listed here in the order of importance.

- A. The county health nurse has obtained information concerning prospective mothers of the type who need care most and has persuaded them of the benefits to be expected from it.

- B. Midwives, closely supervised by local health department units, have persuaded their future patients to seek such care and in some instances have refused to deliver women who have not been examined and pronounced normal by a competent agency.

- C. Patients themselves, whose childbearing has been rendered safer and more comfortable by antenatal instruction, have "sold" their ideas to their friends.

To what extent is prenatal care available to women in isolated and rural districts? The answer to this important question in so far as Maryland is concerned has recently become "Almost completely." As has been said, the paying patient may obtain it from her local physician. The indigent woman may be cared for in prenatal clinics being held regularly under the sponsorship of the Bureau of Child Hygiene, the State Health Department in one or more communities of almost every county in the state. These clinics are held with the approval of the local medical societies, from whose membership the clinic physician is often selected. Many patients are sent to the clinic by their physician, who receives routine reports of the examination. An added function of these clinics is the arranging for hospitalization of the abnormal patient. The major problem at present is that of transportation. In cases to be delivered by a midwife, and upon request by a physician where his patients are concerned, the routine clinic examinations are supplemented by home visits on the part of public health nurses who give advice, seek abnormal symptoms, and assist the patient in pre-

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Collective Review

THE PATHOLOGY OF THE OVARIAN HORMONE

WITH SPECIAL REFERENCE TO ITS ROLE IN TUMOR DEVELOPMENT

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FOR many years various lesions in the female reproductive tract have been attributed by some gynecologists and pathologists to disturbances in the ovarian function. The relationship, however, remained largely theoretical until recently when two new developments made possible more definite methods of investigating it. One was the attainment of potent preparations of the estrogenic substances, which are now available for attempts at the artificial production of pathologic processes in animals. The other was the elaboration of methods of extraction and measurement of the ovarian hormone which can be applied to the study of its effects on human tissues and body fluids.

The pathologic effects produced in animals by the administration of estrogenic substances include particularly the proliferation of the glandular tissues of the secondary organs of reproduction, a metaplasia of columnar to squamous epithelium, hypertrophy of the fibromuscular walls of certain hollow viscera, changes in certain of the glands of internal secretion, and probably the development of some tumors. The human lesions which may be analogous to these are certain hyperplastic and neoplastic conditions of the female and male genital tracts and perhaps changes in certain of the endocrine glands. The study of this field is recent and is still intense, but the knowledge already at hand appears to justify the recognition of a special pathology of the estrogenic or ovarian hormone.

Particularly as the cause for various tumors of the reproductive tract has the ovarian hormone been repeatedly brought before the medical public. As a result it is widely believed that such conditions as endometrial hyperplasia, fibroids of the uterus, and even carcinoma of the breast are "due" to the ovarian hormone. The occasional reader in the subject is too little aware of the varying relationships which lie under this word "due" and of the great gaps and contradictions in the evidence as well as tendencies of investigators to allow facts which merit little more than hypotheses to lead them to more or less definite conclusions.

To be able to evaluate current theories, it is necessary to understand a little about the methods of investigation, upon which the evidence to support them has been based. Two general types of approach have been employed (Table I). The first of these, the older, starts with a given condition, usually a human neoplasm for which an endocrine basis is conceivable. Then evidence is sought to demonstrate a hyperactivity of the ovary. Such evidence may take the form of a histologic investigation of the ovary itself, of a clinical study of the history and physical status of the patient, or a biologic investigation to determine the concentration of the estrogenic hormone in certain tissues or body fluids. This method is always inexact and the data collected capable of different interpretations. Yet this approach is of fundamental importance for one is dealing with the actual lesion whose cause is sought.

The second and newer method has been to begin with a known excess of estrogenic substance and to attempt by its injection, usually into laboratory animals, to produce lesions similar to those of the human being. The method is simple, accurate, and

Society Transactions

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

*NINTH ANNUAL MEETING, DALLAS, TEXAS.
OCTOBER 14 to 16, 1937*

The following papers were presented:

Complete Rupture of the Uterus. Drs. G. W. Gustafson and W. E. Crump (by invitation).

A Comparison of Artificial Fever Therapy and Sulfanilamide Therapy in the Treatment of Gonorrheal Infections in Women. Drs. L. M. Randall, F. H. Krusen (by invitation) and E. G. Bannick (by invitation). (For original articles, see page 230.)

Further Observations on the Role of Streptococcus in So-Called Trichomonas Vaginalis Vaginitis. Drs. G. F. Hibbert and F. C. Falls. (For original article, see page 219.)

Management of Placenta Previa. Dr. David Findley. (For original article, see page 267.)

A Study of the Water, Sodium, and Energy Exchange During the Latter Part of Pregnancy. Drs. R. H. Freyberg (by invitation), R. D. Reekie (by invitation), and C. Folsome. (For original article, see page 200.)

An Analysis of a Human Ovotestis. Drs. James R. Reinberger and C. S. Simkins (by invitation). (For original article, see page 275.)

The Effect of Quinine Upon Auditory Nerve. Dr. Ray A. West. (For original article, see page 241.)

Upper Abdominal Manifestations of Pelvic Disease. Drs. Joseph L. Baer and S. A. Portis (by invitation).

Report of the Committee on Clinical Affairs. Dr. Herbert F. Vanorden.

Personal and Environmental Factors in Obstetrical and Gynecological Practice. Dr. C. M. Campbell.

One-Stage Operation for Resection of the Rectosigmoid and Rectum for Carcinoma (With or Without Hysterectomy). Dr. Jean P. Pratt. (For original article, see page 209.)

The Experimental Production of Ovulation in the Human Subject. Drs. M. Edward Davis and Arthur K. Koff (by invitation). (For original article, see page 183.)

Sterilization of Obstetric Patients in Vanderbilt University Hospital, 1925-1937. Drs. G. C. McClellan (by invitation) and L. E. Burch. (For original article, see page 249.)

A Study of 288 Primiparas Over the Age of 35 Compared With 300 Primiparas Under the Age of 25. Drs. Charles E. Galloway and Tom D. Paul. (For original article, see page 255.)

An Analysis of the Cesarean Sections Performed at the University Hospital of St. Louis. Dr. William C. Stude.

Indications and Contraindications for Cesarean Section. Dr. J. E. Kanatser.

Pelvic Measurements of 4,144 Iowa Women. Dr. William F. Mengert. (For original article, see page 260.)

Artificial Fever Therapy in Pelvic Inflammatory Disease. Drs. M. A. Darling, J. M. Berris, and M. Newman. (For original article, see page 238.)

If evidence by one of these means is found that the estrogenic hormone is in some sense a factor in the production of a given lesion, care must be taken in correctly assessing its importance. In this respect it is useful to note several degrees of relationship.

1. The hormone may play simply a "protective" rôle maintaining the tissue in a state in which some other agent may be effective. This is the simplest explanation of why fibroids do not develop after bilateral oophorectomy.
2. The hormone may be effective only in starting the process, in causing a simple hyperplasia, while other agents are necessary to transform this to a tumor. A possible example of this is the development of carcinoma on the basis of endometrial hyperplasia.
3. The hormone may have certain indirect effects which by producing other types of stimulation lead to tumor formation. The stasis of secretions often noted in mammary ducts in which early carcinoma is present may be the result of a hormone and the cause of a chemical irritation.
4. Finally the hormone may be truly causative, but in two senses. It may represent simply a physiologic stimulus, which when effective excessively produces abnormal morphologic results, or it may be specifically tumor producing. The distinction may not be tenable, but there is probably a difference between the action of "folliculin" which when injected in the skin of the mouse's back produces only mammary tumors and that of certain of the tar derivatives which produce malignant growths in many types of tissue but particularly at the point of injection.

The application of this knowledge of the pathologic effects of estrogenic stimulation to the explanation of human lesions is a tempting field of activity. In this field theory is probably running years ahead of definite proof. In the following pages an attempt will be made to evaluate the evidence which has been brought forward for an estrogenic factor in the production of various lesions.

I. THE FEMALE PELVIC ORGANS

1. *Endometrium*.—For the cystic hyperplasia of the endometrium there exists of course the most complete proof of an estrogenic factor of origin. Here, as elsewhere, the ovarian function was believed to be responsible before the hormone as such had been isolated. It is useful, however, to consider experimental work first.

In the endometrium of laboratory *animals* various changes have been reported following the injection of estrogenic substances. A considerable series of experimenters claim to have produced the typical pattern of the endometrial hyperplasia found in women near the menopause (Zondek;²⁷⁵ Burch, Williams and Cunningham;³⁰ Lacassagne;¹⁵⁴ Zuckerman;²⁸¹ Tietze²⁵⁰). Most workers have employed fairly large quantities of estrone, but in certain animals the amount required may be small. (Simpson and Burch.²³¹)

After long continued injection of these substances other effects are produced which may be analogous to certain human lesions. Metaplasia of the cylindrical into squamous epithelium has been noted by Selye and his co-workers²²⁶ in the uterine horn of the rat and by Lacassagne^{147, 154} in the mouse and rabbit.

Endometrial carcinoma has not been produced by the simple use of an estrogen. Borst²⁰ by combining hormone injection in rabbits with tar painting of the ears obtained a squamous metaplasia of the uterine glands, in places said to resemble cancer. Pierson²⁰⁸ has reported the development in 2 of 25 rabbits injected with corpus luteum and folliculin of an infiltrating cystadenoma having all the characteristics of cancer except metastasis.

Inflammation frequently complicates the picture of estrogen effects on the endometrium, for in rats and mice the vaginal epithelium proliferates so rapidly that the uterus becomes obstructed, drainage ceases, and a pyometra follows. Long-continued experiments with large quantities of hormone are frequently a failure in these animals, owing to their premature death from infections.

easily controlled. To make the evidence valid for an explanation of the human lesion, however, one must make two assumptions: first, that the concentrations of hormone used in laboratory animals are comparable to conditions present in the human subject; second, that the lesion produced is morphologically identical with the human lesion which was the object of study. Both assumptions have been at times too enthusiastically and too hastily made.

TABLE I

OUTLINE OF METHODS OF INVESTIGATION OF THE RELATIONS OF THE OVARIAN HORMONE TO ABNORMAL TISSUE GROWTH

I. With the lesion present and an abnormality in hormone to be sought.

A. Human being:

1. Historical evidence of disturbances in the function of the ovary, as shown in the age of puberty and of the menopause, types of menstrual periods, and fertility.
2. Physical evidence of endocrine dysfunction, as manifested in the other glands of internal secretion, in the degree of development of the sexual organs and, in particular, in the presence of follicle cysts of the ovary and changes in the endometrium.
3. The study of the distribution of multiple tumors, which if they occur in the reproductive tract suggest a common and perhaps ovarian cause.
4. The assay of the estrogenic hormone content of the blood and urine of the patient and of the neoplastic tissue.
5. The search for an hereditary factor which if present indicates an internal, constitutional cause.
6. Observation of the effect of therapy, either the increase of ovarian stimulation by the injection of estrogenic substance or its decrease by castration.

B. Animal:

The study of the reproductive physiology of special strains of animals susceptible to spontaneous tumors is analogous to the methods outlined for the human tumors. Particularly in mice developing mammary cancer, types of estrus cycle, weights and other characteristics of the endocrine glands, the rate of excretion of estrogenic hormone, the hereditary factor and the effects of castration point the way to the studies that are necessary in man.

II. With excessive quantities of hormone available and lesions to be produced.

A. Animal.—In this field with the use of different laboratory animals, with the variation in the amount of estrogenic hormone, and with its association with other factors, the possible combinations of simple experiments become so enormous as to promise research projects for at least a generation of workers. The type of experiments which have been considered already may be outlined as follows:

1. The injection for a variable period of one of the several estrogenic substances.
2. The injection of one of these substances after removal of the sex gland or other organs of internal secretion.
3. The combination of an estrogenic substance with some other hormone, such as progesterone, testosterone, or anterior pituitary.
4. The combination of estrogenic hormone with some irritant, such as trauma, tar, or one of the carcinogenic tar derivatives.
5. The application of any of these principles to animals susceptible and to others resistant to tumor growth.
6. The study of the effect of estrogenic hormone on the rate of growth of spontaneous and transplantable tumors.

B. Human Being.—An attempt to produce fully developed tumors in man by injecting estrogenic hormone is, of course, impractical. Minor effects on the breast and the endometrium, perhaps pathologic, have been reported.

be a complicated one. Suggestions of an endocrine factor are found in reports of a late menopause in many of these cases (Crossen and Hobbs⁶²) and perhaps in the observed association of follicle cysts of the ovary (Taylor). A somewhat promising hypothesis has been offered in the view that endometrial cancer is at times a derivative of endometrial hyperplasia and hence indirectly the result of estrogenic activity. The follow-up studies of cases of endometrial hyperplasia have, however, yielded few established examples of later carcinoma development (Hintze,¹²¹ Mack,¹⁷⁵ Taylor²⁴²). Nevertheless the difficulty which occasionally arises in distinguishing histologically between hyperplasia and carcinoma is well known and isolated examples of carcinoma arising in areas of hyperplastic endometrium have been several times reported (Schröder,²²¹ Meyer,¹⁸¹ Fluhmann and Stephenson⁸³). Two studies (Taylor;²⁴² Novak and Yui¹⁹⁴) of the uninvolved endometria in a series of cases of carcinoma of the corpus uteri have indicated that these glands adjacent to malignant areas are frequently hyperplastic.

2. *Myometrium*.—Myometrial tumors are rare in *animals*, and little experimental work has been undertaken with them. Lacassagne alone has produced what he claims to be myomatous changes in the rabbit and mouse uterus after continuous injection of folliculin. These changes did not, however, take the form of the circumscribed fibromyomas of the human uterus.

The relation of myometrial tumors to the ovary can best be demonstrated from *human* material. Frequent emphasis, beginning at least fifty years ago in an article by Hegar,¹¹² has been given the apparent dependence of the fibromyoma upon the ovary. Its growth is with few exceptions limited to the years of active ovarian function and atrophy usually occurs after the normal or artificial menopause. This demonstration that the ovarian hormone is necessary for the fibroid's existence is, however, no proof that it is directly causative.

Various clinical evidence has been compiled to show defects in the reproductive constitution of myoma patients. These include an alleged high incidence of sterility and dysmenorrhea and the association with other tumors (Freund,⁸⁹ Albrecht⁴).

Pathologic changes in the ovaries of patients with fibroids have, however, been the chief evidence upon which the theory of an ovarian cause has been based. This work is often dated from a paper of Seitz²²³ in 1911, but Popow²⁰⁹ writing in 1890 cites seven authors who had already considered the subject. The changes in the ovary reported have been extremely varied, consisting in enlargement of the whole organ, increase in the stroma and vessels, hyaline changes in vessel walls, lipid deposits, and particularly "cystic degeneration" (Popow,²⁰⁹ Bulius,²⁷ Mayer,¹⁷⁷ Moretti,¹⁸⁵ Albrecht⁴).

The chief protagonist of the ovarian theory in recent years has been Witherspoon.²⁶³ He believes that "hyperestrinism," when acting over a short time, results in hyperplasia of the endometrium, when over a long time, in fibroids. He based his case on the frequent association in the same patient of cystic ovaries, myoma and endometrial hyperplasia. The evidence of Witherspoon can be attacked on two points, the strictness of his interpretation of the term hyperplasia, and the general frequency of follicle cysts. Häggstrom¹⁰⁸ for example in an extremely detailed study of 54 cases of fibroids found hypertrophy of the endometrium in only 4, and in his opinion cystic changes were present in the ovaries in no unusual frequency.

The finding of estrogenic hormone in considerable quantities in fibroids is of great interest (Courrier,⁵⁵ Lewis and Geschickter¹⁶⁴). The significance of the observation certainly depends upon whether this high concentration is specific for tumor tissue or may be, as Frank⁸⁵ and his co-workers have suggested, not greater than that of certain normal tissues in women.

A strong stand against an ovarian dysfunction as a cause of fibroids is taken by Meyer.¹⁸⁰ He points out that patients with fibroids usually menstruate normally unless the position of the growth causes the bleeding, that they may become pregnant, and that no corpus luteum deficiency is demonstrable, because the endometrium often shows a pregravid mucosal pattern. Some dependence on the ovary is probable, but this may be effective through the vascular supply. Fibroids with extensive vascular adhesions to abdominal organs may continue to grow after the menopause in the presence of atrophic uterus and ovaries (Dichtl¹⁶⁸).

Hyperplasia of the human endometrium was first referred to as ovarian dysfunction by Brennecke²⁴ in 1882, and since the work of Schröder²²¹ in 1915 an ovarian origin has been generally accepted. This condition remains today the most perfect example of a proved morphologic change resulting from an ovarian dysfunction in the human body, although some of the details of its mechanism are still disputed.

Schröder believed that a persistent unruptured follicle exerting its influence over an abnormally long period of time produced the hyperplastic changes. He was able to show in a number of cases the presence of hyperplasia of the endometrium, the existence of a large unruptured follicle in the ovary and an absence of any recent corpus luteum. Meyer¹⁸² believed the condition due to a series of rapidly developing follicles, coming too close together for orderly ovulation and corpus luteum formation.

The condition of the ovaries associated with a hyperplasia of the endometrium has been studied by a long series of investigators (Babes,⁸ Novak and Martzloff,¹⁹³ Beckman,¹² Shaw,²²⁷ Graves,¹⁰⁶ Fluhmann⁸²). Their work has tended to confirm the presence of one or more unruptured follicles and with a few exceptions the absence of fresh corpora lutea. The morphology of the endometrium too supports the view that the disease is due to an excessive or prolonged stimulation by an estrogenic hormone in the absence of any corpus luteum activity.

The attempts to demonstrate excessive estrogenic substance in the body fluids of patients with endometrial hyperplasia have not met with invariable success. Frank⁸⁵ and his co-workers noted an increase of female sex hormone in the blood and urine of patients with abnormal bleeding at puberty and before the menopause. Zondek²⁷³ has shown the hormone to be present in excessive amounts in the fluid content of the follicular cysts and in the urine during the amenorrheic phases of polyhormonal amenorrhea associated with cystic hyperplasia. Siebke²²⁸ found estrone in the blood especially during phases of nonbleeding.

The best examples of the dependence of hyperplasia of the endometrium upon estrogenic substance are found in the cases of granulosa cell tumor, new growths which are known to form estrogens (Schuschiana²²²) and which are always associated with endometrial changes. The production of hyperplasia in castrate women by the injection of estrogenic substances has also been accomplished (Werner and Collier²⁵⁷).

That the ovarian changes may not be the primary lesion but the disease actually dependent upon some disturbance of the anterior pituitary has been suggested by some workers (Hofbauer;¹²⁴ Burch, Williams, Wolfe and Cunningham³¹).

Some uncertainty has entered with the recognition of the occurrence of hyperplasia of the endometrium in women many years after the menopause. Reports of isolated cases of this type have been in the literature for some years (Seitz,²²³ Meyer¹⁸⁰), and recent articles have suggested that this may be of not infrequent occurrence. Breipohl,²³ who studied the endometria of 130 women in the menopause, noted hyperplasia in 15 or 11.53 per cent. In a recent study of patients with postmenopausal bleeding (Taylor and Millen²⁴⁶) there were found among 35 women, having no tumor or inflammatory lesion in the pelvis, 4 cases of bleeding from a hyperplastic endometrium developing four to thirteen years after the menopause. The explanation of this late hyperplasia is not clear. It may result from local causes unrelated to the ovarian function. Late follicular development may occur and perhaps be the source of estrogenic hormone. A small granulosa-cell tumor, undetected by the surgeon, is an occasional cause of late hyperplasia of the endometrium. An extraovarian source of an estrogenic substance is a final possibility.

Islands of squamous epithelium are well known to occur in the endometrium (Fluhmann⁸²) and perhaps are the counterpart of the squamous metaplasia developing in laboratory animals after treatment with estrogens. Their special tendency to be associated with endometrial hyperplasia (Hintze¹²⁰) is a little support for the view that these islands of squamous epithelium in the human uterus are estrogenic effects. That the squamous metaplasia found in some cases of endometrial carcinoma, the so-called adenoacanthoma, has a similar factor in its origin is at least a possibility.

Carcinoma of the endometrium has its peak of incidence some years after the menopause and any relation which may exist to the ovarian hormone must apparently

To associate cancer of the human cervix even remotely with the ovarian hormone will require more proof than is at present available. The disease occurs in a tissue which one is accustomed to associate less intimately with endocrine reactions than is the case with the endometrium or the breast epithelium. The coincidence of tumors of the endometrium and myometrium has been frequently reported, but cancer of the cervix appears to stand as a separate lesion.

Nevertheless an effort has been made to introduce the ovarian hormone into the background of human cervical cancer. Hofbauer¹²⁵ in particular has suggested that the well-known predilection of cervical cancer for multiparas is not due to the inflammations resulting from traumatic lesions occurring at delivery, but to the excessive hormone stimuli which the cervical epithelium is subjected to during pregnancy. As direct evidence of this latter effect, he has observed in biopsies of the cervix during pregnancy an unusual activity of the squamous epithelium. These views gain in weight when coupled with the growing evidence offered in the work of Schiller,²¹⁶ Hinselmann,¹¹⁹ and others that areas regarded as precancerous are not as a rule in regions of maximum inflammation and may be in the midst of apparently normal epithelium.

Frequent observations of increased gonadotropic hormone in the urine of patients with cancer of the cervix are perhaps to be explained by the fact that most of these patients are in the menopause. The occasional reports of increased estrogenic hormone (Imbert, Mosinger and Bontoux,¹²⁸ Schön²¹⁸) seem difficult to reconcile with other knowledge of the disease. Other observers have in fact failed to note (Kosakaé Ohga and Okamoto¹⁴²) significant changes in the estrogenic excretion of cases of uterine cancer.

II. THE MAMMARY GLAND

It is in the mammary gland, however, that the most interest is centered at present and in the study of which most recent progress has been made. This can be traced directly to the fact that strains of mice are available for experimentation in which there is a high incidence of spontaneous, hereditary mammary cancer. The striking relationship between the ovarian function and the development of these laboratory carcinomas has led to a somewhat frantic effort to force human breast tumors into an identical category.

a. *Chronic Mastitis*.—The term chronic mastitis is a very loose one, having a different meaning to the clinician, to the pathologist, and to the experimental investigator with animals. To the clinician it includes practically all the diffuse benign breast conditions, manifested by pain, nodules, and discharge. To the pathologist it is a variety of conditions with four special features, namely epithelial hyperplasia, fibrosis, cyst formation, and small collections of lymphocytes and other cells suggestive of a chronic inflammation. Many workers with the lower animals apparently feel that all they need to do in order to reproduce chronic mastitis is to show some epithelial hyperplasia and possibly the cystic dilatation of a few ducts.

The production of lesions in animals, similar to the spontaneous chronic mastitis in the human being has been reported by numerous workers after the injection of one or several hormones (Goormaghtigh and Amerlinek,¹⁰³ Wieser,²⁶¹ Cramarossa⁵⁷). In a recent series of experiments undertaken on rats Herold and Effkemann¹¹⁷ have concluded that lesions similar to human chronic mastitis arise from excessive amounts of follicle hormone in the absence of corpus luteum. Others have been more hesitant in the use of the term chronic mastitis but have reported, following the protracted administration of an estrogen, atypical cellular growth preceding the development of cancer in mice (Lacassagne,¹⁴⁶ Burrows,³⁴ Bonser,¹⁸ Gardner and others⁹¹). MacDonald,¹⁷³ however, working with rabbits noted a definite limit to the proliferation of ductal epithelium which could be produced by theelin and corpus luteum extract beyond which a refractory condition was set up. He concluded that these substances did not produce specific pathologic lesions such as cystic diseases or adenosis.

Turning to a review of the studies of human material, one finds that an ovarian disturbance has frequently been offered as an etiologic factor. Suggestions made in this direction are nearly a century old and several good contributions, notably that of Moszkowicz¹⁴⁷ in 1927, definitely preceded the isolation of the sex hormones.

3. *Endometriosis and Adenomyosis.*—The controversy over the source and route of transportation of abnormally placed endometrial tissue has overshadowed the consideration of why the ectopic endometrium should grow. The relation of the estrogenic hormone to these lesions is, however, of some theoretical importance.

a. *Endometriosis of the ovary and peritoneum (Adenomyosis externa):* Experimental work on endometriosis has centered chiefly on certain disputed points of the Sampson theory. It has been shown beyond question that fresh bits of rabbit endometrium implanted upon the peritoneum will grow (Jacobson¹³⁰). Experiments indicate also that the growth of implants is less extensive in the absence of the ovaries (Brakemann,²² Katz and Szenes¹³⁵) and that atrophy of the implants can be prevented by injection of estrogen (Gleave¹⁰¹).

A theory postulating an ovarian factor in the origin of human endometriosis, based largely on clinical data, has also been developed. In its general implication this has been supported by numerous writers (Lauche,¹⁶² Adler,² Meyer¹⁸⁰). That the disease develops during the years of active ovarian function is an important fact. That atrophy occurs after the artificial menopause has been demonstrated, especially by Graves.¹⁰⁶ The association with other uterine new growths, particularly adenomyoma and hyperplasia of the endometrium, suggests a common origin for all (Smith,²³³ Allen,⁵ Jeffcoate and Potter¹³¹). Abnormalities of the ovaries, such as follicle cysts (Witherspoon²⁶³) and an absence of corpora lutea (Jeffcoate and Potter¹³¹) have been stressed as factors in the cause of endometriosis, as for so many other neoplastic lesions in the reproductive tract. The association of endometriosis with granulosa cell tumors has been reported (King¹³⁷).

If, as has been maintained, carcinoma, particularly of the ovary, is sometimes a derivative of endometriosis (Sampson,²¹⁵ Reinhardt,²¹¹ Höppner¹²³), then for this malignant tumor an indirect relationship with the ovarian hormone is a possibility.

b. *Adenomyosis of the uterine wall:* The infiltration of the uterine musculature by endometrial tissue is another of the lesions limited to the later years of ovarian activity. An earlier inflammatory theory of origin has gradually been replaced by a vaguer conception of a decreased resistance of the myometrium against the invasion of mucosal tissue (Frankl⁸⁶) and a pathologically increased regenerative capacity developed by the mucosa as a result of the repeated demands made upon it through menstruation (Meyer and Kitai¹⁸¹). Several writers have in general terms invoked the ovarian hormone as a factor (Meyer,¹⁸⁰ Albrecht,⁴ Adler²). Pathologic changes in the ovaries (Adler,² Jeffcoate and Potter¹³¹), association with a granulosa cell tumor (Tietze²⁴⁹), and the coincidence of hyperplasia of the endometrium (Novak and Martzloff,¹⁹³ Jeffcoate and Potter¹³¹) have been noted as a part of the pathologic background of adenomyosis of the uterus.

4. *Cervix:* There appeared in 1933 a startling report by Overholser and Allen¹⁹⁹ who claimed to have produced a lesion resembling early cancer of the cervix in monkeys. This had been accomplished by trauma to the cervix associated with the injection of estrogenic substances. The importance of these studies depended to a large extent upon the histologic interpretation of the cervical lesions, for none of the supposed early cancers had infiltrated or metastasized. The work of Overholser and Allen has now been repeated in several species of animals (van Wagenen,²⁵² Zuckerman,²⁸¹ Herold and Effkemann,¹¹⁶ Loeb and his co-workers,¹⁶⁹ Engle and Smith,⁷⁹ Hisaw and Lendrum¹²²). The development of metaplasia has been confirmed, but the close relation to cancer is now denied by most workers. Overholser and Allen²⁰⁰ themselves in a subsequent paper classed the process simply as a hyperplasia.

Actual cancer of the cervix has been reported in three mice treated simultaneously with theelin and 1:2:5:6 dibenzanthracene (Perry and Ginzton²⁰⁴), but here the relative importance of the two factors is difficult to determine.

Squamous metaplasia is not an uncommon finding in the human cervix, although usually ascribed to the irritants of chronic inflammation (Fluhmann⁸²). That the ovarian hormone contributes to the change appears not improbable after a consideration of the experimentally produced lesion just described. A case of extreme epidermidalization of the cervical glands associated with a granulosa cell tumor recently came under my observation.

breast tissue to concentrate estrogen within itself (Lewis and Geschickter¹⁶⁷). Doubt has been cast on this work by the observation of Frank⁸⁵ and his co-workers that similar large amounts of estrogen may be found in the normal uterus and even in the psoas muscle.

Recent carefully controlled studies of Mohs¹⁸⁴ indicate very low amounts of estrogenic substance in the rat adenofibroma and even when large amounts are administered, the concentration does not arise above that in the striated muscle.

c. *Mammary Carcinoma*.—The series of experiments which have demonstrated the relation of carcinoma of the mammary gland in mice to ovarian function began with the work of Lathrop and Loeb¹⁶⁰ in 1913. These workers showed that in a cancer-susceptible strain the tumor incidence could be lowered and the average age of appearance raised by the prevention of breeding and by castration. This work was amplified by Loeb¹⁶¹ in 1916 and corroborated by Cori¹⁵³ in 1927.

A new principle was introduced in 1928 by Murray¹⁹⁰ when he produced mammary cancer in male mice. Male mice, even in susceptible strains, are ordinarily entirely free from mammary cancer. Murray produced such tumors by transplanting into male mice ovarian tissue. This principle was extended by Lacassagne when he also produced mammary cancer in male mice of susceptible strains by injecting estrogenic substances.

The experiment by which mammary cancer has been produced in males of a susceptible strain has now been repeated many times (Burrows,³⁶ Cramer and Horning,⁵⁹ Gardner,^{91, 92} and his co-workers, Bonser,¹⁸ Suntzeff and others,²³⁶ Korteweg¹⁴¹). In the most recent reports of Gardner and his associates⁹⁶ it is noted that mammary carcinoma may develop in male mice following the injection of a variety of estrogenic substances, theelin, equiline benzoate, ketoestrin benzoate, and hydroxyestrin.

Although the estrogenic substances are clearly an important factor in the production of mammary cancer in mice, an hereditary predisposition remains, as is shown by the greater incidence and earlier appearance of estrogen-induced mammary cancer in male mice of strains in which the females are spontaneously susceptible (Lacassagne,^{148, 156} Bonser,¹⁷ and Suntzeff and others^{236, 237}). In a recently reported series of injections by Lacassagne,¹⁵⁶ of combined hormones into a series of mice refractory to mammary carcinoma, a variety of tumors appeared, but not of the mammary glands. Cancer may nevertheless occasionally appear in relatively resistant strains after prolonged estrin injections (Gardner, Smith, Strong and Allen⁹⁶).

The basis for this predisposition of certain strains of mice to the development of mammary carcinoma is perhaps to be found in some constitutional peculiarity of the reproductive system. Relatively little attention has, however, been given the comparative study of the endocrine organs of these different strains. What efforts have been made have been directed chiefly toward the lengths of the estrus cycles, but although differences have been claimed (Lacassagne¹⁵⁷), these have not been generally recognized (Bonser,¹⁷ Burns, Moskop, Suntzeff and Loeb³²).

Lacassagne¹⁵⁷ has in addition noted differences in the pituitaries and Cramer and Horning⁶⁰ a peculiar "brown" degeneration of the adrenals in mice of high tumor strains. Barry and Kennaway have reported some differences in the response of the thyroid gland of different strains to estrone. That variations in function of the individual animals may within a given strain affect the incidence of mammary cancer is clear from the long-recognized fact that cancer is more frequent in breeding than in virgin females (Lathrop and Loeb,¹⁶⁰ Bagg¹⁰). Whether this increased incidence is due to the irritating effects of the products of secretion or to the continuous hormone stimulation of the pregnancies is not clear. Murray has recently reduced the incidence of mammary cancer in female mice by joining them in parabiosis with a male. The effect of this experiment was to alter the estrus cycle and produce certain changes in the ovaries presumably by the introduction of the male hormone.

The finding of hormones in the tissues or the secretion of various types of diseased breast is at present of debatable significance. Substances resembling both the anterior pituitary and an estrogenic hormone have been isolated from mouse mammary carcinoma. (Dobrovolskaia-Zavadskaia and Zéphiroff.⁶⁹) Lewis and Geschickter¹⁶⁸ found little or no estrogenic substance in human mammary cancer.

Lately numerous writers, resting their case rather heavily on an analogy with the animal experiments, have proclaimed the ovarian origin of human chronic mastitis (Lewis and Geschickter,¹⁶⁶ Cheattle⁴⁷).

To complicate the problem there appear to be at least two rather strongly contrasted clinical forms of so-called chronic mastitis. First, there is the type with discharge, usually of a milky or oily character, from the nipples. This is regularly associated with a stasis of secretions in the terminal portions of the ducts, giving a nodular consistency to the central area of the breast. On physiologic grounds this type might be ascribed to an excessive stimulation by one of the anterior pituitary hormones. In the second type there is instead of secretion marked pain and engorgement before the menstrual periods. With this form there may be a general hypertrophy or a nodularity usually restricted to the outer quadrants.

Based upon a clinical study of the ovarian function of a series of patients with chronic mastitis (Taylor²⁴³) certain points may be made. A functioning ovary is apparently essential for the persistence of the simple painful type of mastitis, because the disease rapidly improves with the menopause. This relationship is less striking when discharge from the nipple is a prominent feature, for the secretion may continue for several years after the cessation of the ovarian function. Frequent disturbances in menstruation, especially decreased flow and a prolonged interval, are present in patients with each form, but particularly with the secretory type. Cystic ovaries are often found, but changes in the endometrium rarely. Bio-assays of the blood and urine of these patients for the estrogenic hormone reveals no consistent increase or decrease in the ovarian activity.

A somewhat incomprehensible aspect of this subject has been the persistent reports of favorable results obtained by treatment of chronic mastitis with various hormones (Cutler,⁶⁴ Whitehouse,²⁵⁹ Dahl-Iversen,⁶⁵ Rogers and Nathanson,²¹² Gernez and Gernez,⁹⁸ Cotte,⁵⁴ Lewis and Geschickter¹⁶⁸). Many observers blame the symptoms on the corpus luteum and insist on ovarian preparations free of progesterin. Bérard,¹³ however, deliberately gave corpus luteum and obtained good results. Geschickter and Lewis recommend estrogenic substance alone to control the formation of cysts and this plus lactogenic substance for 'adenosis.' On the contrary Werner and Collier²⁵⁷ have produced enlargement and discomfort of the breasts by giving theelin to castrated women and excellent results may certainly be obtained by reducing the patient's normal estrogen supply by radiation of the ovaries (Taylor and Brown²⁴⁵).

b. *Mammary Fibroadenoma*.—Experimental work on the fibroadenoma has centered not on the mouse, but on the rat where fibroadenoma occurs spontaneously and is easily transplantable. A number of workers have shown that the morphology of the transplanted tumor varies markedly with the sexual status of the animal. Before puberty in females and in adult males the tumor tends to be a fibroma, while in females of litter-bearing age glandular hyperplasia with a tendency to cyst formation may be prominent (Heiman and Krehbiel¹¹³). Changes in these tumors in pregnancy and lactation are well known (Emge and Wulff,⁷⁵ Grauer and Robinson,¹⁰⁴ Heiman and Krehbiel¹¹³). Picco²⁰⁷ has reported sarcomatous changes after the injection of theelin.

The question of the actual production of new tumors by estrogenic hormone injections is somewhat clouded by the spontaneous occurrence of such tumors in a frequency said to amount to about 8 tumors in 1,000 animals. Heiman and Krehbiel,¹¹³ however, found five such tumors among 75 animals injected with a combination of theelin and antuitrin-S or -G. Evans and Simpson⁸¹ have also reported a high incidence of fibroadenomas in rats injected over long periods of time with anterior hypophyseal substances.

For the human fibroadenoma an estrogenic substance is perhaps also essential, for the tumor does not occur before puberty and its new development is rare after the menopause. Histologic changes in the morphology of the tumor occur with pregnancy, lactation (Hunter,¹²⁷ Kilgore,¹³⁶ Kreibig¹⁴⁴), and perhaps with the menstrual cycle (Ingleby¹²⁹). The occurrence of a high concentration of estrogenic substance in the tissues of human fibroadenomas has been reported and made the basis of a theory that the origin of the tumor is based on the ability of a local area of

In mice subjected to treatment by estrogenic substances there occurs especially in the so-called coagulating gland a metaplasia of the columnar to squamous epithelium, desquamation of cells into the lumen and an invasion with leucocytes (Burrows,³⁵ de Jongh^{132, 133}). Several observers have noted that in the monkey treated by an estrogen, there develops an increase in the fibromuscular stroma, perhaps even a decrease in the epithelium, except for a stimulation or metaplasia of the epithelium of the prostatic utricle and adjacent areas of the urethra (van Wagenen,²⁵² Zuckerman and Parkes²⁸³). It may be questioned, however, how far these changes in the lower animals correspond morphologically with those observed in prostatic hypertrophy in man.

In mice these effects of estrogenic injections may be very widespread and Burrows³⁵ has described definite gradients of susceptibility, vestigial cysts being first affected, then the coagulating glands, next seminal vesicles and the prostate in that order. In all of these glands as well as the ejaculatory ducts the changes begin and are most marked nearest to the urethra. When estrone is withdrawn, these changes are reversible, but the return to normal begins in the peripheral portions and progresses toward the urethra. Lacassagne¹⁴⁸ has suggested that this selective estrogenic action may have an embryologic explanation, since portions of the dorsal wall of the urethra and its outgrowths may be derivatives of the Müllerian ducts. This might account for the similarity of this response to that of the vagina.

An interesting series of experiments have shown that these estrogen-produced changes may be prevented by giving various substances, particularly the male hormone (Korenchevsky and Dennison,¹⁴⁰ Rusch,²¹⁴ Overholser and Nelson,²⁰¹ Zuckerman, Zuckerman and Parkes, de Jongh^{132, 133}). Burrows⁴² obtained similar results with corpus luteum, but de Jongh did not. These observations have given rise to the theory that prostatic hypertrophy in man may be due to a hormone imbalance and a predominance of the estrogenic hormone (Korenchevsky and Dennison,¹⁴⁰ Zuckerman,²⁸⁰ Niehans and others¹⁹²). A somewhat different type of imbalance is proposed by Lower, Engel and McCullagh¹⁷¹ who believe the hypertrophy due to a relative decrease in "inhibin," a hormone produced by the tubular cells of the testes in relation to "androtin," a substance elaborated by the interstitial cells.

Some material is undoubtedly at hand to support a theory that the estrogenic hormone is a factor in the production of benign prostatic hypertrophy even in man: (a) It is known that the human prostate responds to the estrogenic hormone. This is particularly demonstrated by the swelling of the prostates of the newborn at a time when the estrogenic hormone is known to be present in the circulation. Areas of squamous epithelium are also found in the prostates of the newborn and in young infants (Aschoff⁷; Schlachta²¹⁷); (b) substances like the ovarian hormone undoubtedly occur in the male throughout life, as has been demonstrated by numerous workers (Oesterreicher,¹⁹⁷ Koch,¹³⁹ Zondek and Euler,²⁷⁷ Glimm and Wadehn,¹⁰² Bühler²⁶).

Studies of the urine of men suffering from benign prostatic hypertrophy have not, however, shown an abnormal excretion of the estrogenic hormone (Owen and Cutler²⁰²). Other workers (Hamilton,¹¹¹ Deming⁶⁷ and Allen⁵) have failed to find estrogenic material in either the urine of patients with the disease or in the tissues of surgically removed prostates. Rusch²¹⁴ and Kundert¹⁴⁵ alone report that they have evidence that in men with enlargement of the prostate the male hormone is decreased in proportion to the estrogenic hormone.

The various theories of origin have given rise to a variety of endocrine treatments for prostatic hypertrophy. Castration was formerly occasionally employed (White²⁵⁸), but this operation fell into probably deserved disuse. Deming⁶⁷ and his co-workers describe a recent failure of such therapy and offer a reason for this failure, based on embryologic and physiologic grounds. Niehans¹⁹² advocates ligation of the vas deferens, which is claimed to result in hypertrophy of the interstitial cells and thus in an overcoming of the excess of follicular over male hormone. Zuckerman²⁷⁹ has reported some success in the giving of male hormone in the form of testosterone propionate. Lower, Engel and McCullagh,¹⁷¹ however, have noted a 65 per cent rate of improvement in 40 cases of prostatic hypertrophy treated with "inhibin," to reduce activity of the interstitial cells and prevent the excess of male

The evidence for an endocrine factor in human breast cancer is very difficult to evaluate.

1. The age incidence has an important bearing on etiologic theory. Approximately a third of the cases of breast cancer occur in women with a mature menstrual function. Another third occur within a ten-year period of theoretically unstable ovarian function during the five years preceding and the five years succeeding the menopause. In the older women, who represent the last third, any development of carcinoma from the ovarian hormone must presumably depend on the continued development of abnormal cellular material having its inception many years before.

2. Strong evidence now exists that there is an hereditary factor in breast cancer (Wainwright,²⁵⁴ Waaler,²⁵³ Wassink,²⁵⁵ Cramer⁵⁸). This points at least toward an intrinsic factor which is quite conceivably an inherent peculiarity of reproductive physiology.

3. Large series of statistics have shown that cancer of the breast occurs relatively more frequently in nulliparous women (Lane-Claypon¹⁵⁰). This is in direct contrast with what has been observed in hereditary mouse carcinoma.

4. Lactation deficiencies occur with considerable frequency in the history of women with breast cancer (Adair¹). The significance of this observation is not clear. Perhaps the failure to nurse is voluntary and the stasis of secretions produces irritation and cancer. Perhaps the failure to nurse is a physiologic deficiency based on some functional or structural abnormality, associated also with the cause of the breast cancer.

5. Menstrual disturbances have been reported with some frequency in young women with breast cancer (Lane-Claypon,¹⁵⁰ Taylor²⁴³). Olch¹⁹⁸ has noted a delay in the appearance of the menopause. These observations again may indicate a physiologic state favorable to abnormal epithelial proliferation.

6. Two or more tumors developing in separate organs of the reproductive tract decidedly suggest a common etiologic factor, and there appears certainly to be an unexpected frequency of association of pelvic and mammary tumors. Schreiner and Welr²¹⁹ noted cancer of the breast and cancer of the female pelvic organs in 18 of 307 instances of multiple tumors. Meigs¹⁷⁸ noted that 10 per cent of 250 multiple tumors were combinations of a breast and pelvic growth. Taylor²⁴⁴ has previously reported the special frequency of association of breast and endometrial carcinoma and isolated case reports of the coincidence of these two tumors are to be found in the literature (Seliga,²²⁴ Esch,⁸⁰ Smith and Bartlett²³⁴). The association of cancer of the breast and the cervix has likewise been noted (Sitzenfrey,²³² Cordua,⁵² Hellendall^{114, 115}) as well as various mammary tumors with uterine fibromyoma (Taylor²⁴³).

7. Although the evidence for an endocrine cause for breast carcinoma is confusing, there are plenty of observations to show the effects of the ovarian hormone on already established breast cancer. There is first the widely held belief in the rapidity of growth and grave prognosis in breast cancer developing during pregnancy or lactation. Second there is the effect of suppression of the ovarian function. Bilateral oophorectomy as a method of treatment of recurrent breast cancer had a brief vogue forty years ago (Beatson¹¹). This principle has been revived in recent years in the form of radiation castration (Ahlbom,³ Hoffman,¹²⁶ Dresser⁷²) which appears to be successful at times in causing a temporary regression of bone metastases. The relatively low incidence of carcinoma of the breast in women who have had their ovaries removed (Herrell¹¹⁸) suggests at least that the ovarian hormone favors carcinoma of the breast by preventing epithelial atrophy.

III. MALE GENITAL ORGANS

a. Prostate.—Striking changes occur in the male genital tracts of animals treated over long periods with estrogen. These changes affect particularly the prostatic glands and have given rise to various theories of origin for human prostatic hypertrophy. Difficulty is at once encountered, however, because the complicated embryology of the human prostate makes it difficult to relate it to the very differently constructed, although perhaps similarly functioning, glands of the lower animals.

Similar changes in the adrenals have been reported in less detail by other workers (McEuen and others,¹⁷⁴ Selye and Collip,²²⁵ Cramer and Horning,⁶¹ Ellison and Burch⁷⁴). The spontaneous appearance of this degeneration in mice of a strain with a high incidence of mammary carcinoma has been observed by Cramer and Horning.⁵⁹ It perhaps represents the first anatomical demonstration of a peculiarity in the endocrine constitution of these mice predisposed to mammary cancer.

c. Testis.—In general the estrogenic hormone appears to arrest spermatogenesis, perhaps by inhibition of the anterior pituitary. Various estrogens, notably equilin, dihydroxyestrin, and to some degree trihydroxyestrin, when given to mice, cause multiplication and swelling of the Leydig cells (Burrows³⁸). These become loaded with some material, probably of a fatty nature, and tend in places to coalesce and form giant cells with several nuclei. As this interstitial tissue increases, the tubular epithelium is destroyed until only a single layer of cells remains. A group of other workers have observed varying degrees of testicular atrophy in different laboratory animals. (Lacassagne,¹⁵¹ Frazier and Mu,⁸⁷ Halpern and D'Amour,¹⁰⁹ Cramer and Horning.⁶⁰)

d. Ovary.—When large amounts of estrogenic hormone are available, follicle ripening is also delayed. This is presumably on account of the inhibiting effect of the estrogenic substance upon the anterior pituitary, for the pituitaries of animals receiving ovarian hormone are less potent, when implanted, in producing sexual maturity in immature female rats than are those of untreated animals (Leonard, Meyer and Hisaw,¹⁶³ Biale-Laprida¹⁶).

Certain apprehension has been felt as to the effect of therapeutic doses of the estrogens on the human ovary, especially when given to children. Allen and Diddle⁶ have shown that following large doses to immature monkeys there was an immediate slight decrease in size of the ovaries as a result of a smaller number of large follicles, but that a month later this difference between the ovaries of treated and untreated monkeys had disappeared.

V. THE SOURCES OF ABNORMAL ESTROGENIC HORMONE IN THE HUMAN BODY

From a consideration of the lesions described in the foregoing pages, several points should be clear. First, there exists ample evidence to show that immense quantities of the estrogenic substance when given to laboratory animals produce a series of changes including proliferation and metaplasia of specific tissues, some incidental inflammatory processes and various reactions in certain endocrine glands. Second, there can be found a series of lesions in human pathology which are perhaps, even probably, analogous to the experimentally produced estrogenic lesions in animals. The final proof that the latter are also due to estrogenic stimulation depends on the demonstration of some excessive activity of the estrogenic hormone in man. This has not been satisfactorily accomplished, however, for any human lesion with the possible exception of endometrial hyperplasia. For the other conditions the evidence, outside of that offered by their morphologic similarity to the estrogen-produced lesions in animals, is simply suggestive.

If one is to compare the human lesions with those of animals, it is necessary to consider sources of an abnormal hormone supply or a means by which the hormone may be abnormally effective. At the outset it must be emphasized again that the quantities injected into small laboratory animals must produce a temporary blood concentration beyond anything which may at any time conceivably exist in the human body. To this important objection several answers may be given.

1. Animal experiments are in general relatively short. It is possible that the estrogenic hormone acting in small quantities for over fifty years in the human organism may produce effects similar to those brought about by large doses in six months in the mouse.

2. It is possible that susceptible tissues or cells store or fix these substances in concentration far above that of the rest of the body. Some evidence already exists for the latter in the reported observations of large quantities of estrogen in the tissues of certain tumors.

hormone. The inherent contradictions in the rationale on which these various procedures are based cast a doubt on the results reported for all of these methods of therapy.

b. Seminal Vesicles.—The effects upon the seminal vesicles which have been reported to follow estrogen injections are somewhat paradoxical. Most workers agree that an increase in weight of the seminal vesicles is due simply to an hypertrophy of the muscular walls, for the epithelium may even be somewhat reduced in amount (van Wagenen,²⁵² Overholser and Nelson²⁰¹ Freud⁸⁸).

c. Scrotal hernias have been observed by several experimenters, particularly Burrows,³³ to occur in male mice treated for about ten weeks by the continuous administration of estrogenic substances. Burrows regards them as due to a relaxation of those layers of muscle which regulate the caliber of the passageway between the abdominal cavity and the scrotum.

d. Urinary retention develops in male mice treated with an estrogen and according to Burrows and Kennaway⁴⁴ is probably due to hypertrophy of the prostate. Similar observations were made by Lacassagne.¹⁵³ Chronic distention of the bladder with a secondary hydronephrosis develops in many of these animals and may terminate the experiment prematurely.

IV. EFFECTS OF THE ESTROGENIC HORMONE ON THE ORGANS OF INTERNAL SECRETION

The effects of the estrogenic hormone described to this point have been in general of a stimulating character, producing proliferation or metaplasia in the secondary organs of the male and female reproductive tracts. Besides these widely studied changes, there have been noted various reactions in the organs of internal secretion. The great majority of these effects have been observed only in animals and knowledge of their human counterparts is largely lacking. The nature of these changes is often not clear, being sometimes perhaps an hypertrophy but at other times having the character of atrophy or degeneration. These changes in the endocrine glands are perhaps themselves essential links in a chain of reactions which is set off by increases in the estrogenic hormone.

a. The Anterior Pituitary.—It has long been recognized that the ovary had a so-called inhibiting effect on the anterior pituitary gland, and it is well known that with removal of the ovaries there may occur a pituitary hypertrophy with, in some species, the appearance of so-called castration cells, enlarged basophiles containing globules of a colloid-like substance. Numerous investigators have shown that these castration changes can be prevented by the administration of estrogen (Wolfe and Chadwick²⁷⁰). When large amounts of estrogenic substance are given, there is a degranulation of the eosinophilic and basophilic cells and an increase in size and number of the chromophobe cells (Nelson;¹⁹¹ Wolfe and Phelps²⁷¹). With the administration of immense doses to rats and mice over long periods of time, there may develop adenomas of the chromophobe cells. This change was noted particularly by Cramer and Horning,⁵⁹ who observed these tumors in three, and a diffuse enlargement in eight, of twelve mice treated with an estrogen over a period of several months. The physiologic condition resulting appears to be one of hypopituitarism. Such tumors in animals have been observed after estrogen injections by several other workers, notably Zondek,²⁷⁶ Burrows,⁴³ McEuen and others,¹⁷⁴ and by Selye and Collip.²²⁵ Oberling¹⁹⁵ noted adenomatous areas in the hypophyses of castrated rats into which ovarian tissue had been grafted. Gardner, Strong and Smith⁹² observed a chromophobe adenoma in an untreated female mouse which bore also bilateral granulosa cell tumors of the ovary and multiple mammary carcinomas.

b. Adrenals.—When estrogen is administered in large quantities to mice, characteristic effects are produced in the adrenals. These changes appear first as an increase in the thickness of the cortex with the development of a so-called x zone at its inner margin. Next there occurs an increase in the vascular connective tissue lying between the cortex and medulla and finally in the same region the accumulation of lipid-like substances in the inner cells of the zona fasciculata which eventually coalesce to form poorly staining masses containing scattered nuclei (Burrows⁴¹).

side of the ovary, and so be effective in males as well as in females after the menopause. (2) Disturbances in the normal chemistry of either the sex hormones or of the bile acids might result in the formation in the body of chemically related carcinogenic substances. The latter possibility has already given birth both to hypothesis and to caution against premature judgment (Cook and Dodds,⁴⁸ Dodds,⁷¹ Loeb,¹⁶⁹ Thomson²⁴⁸).

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3. Finally, the tissues in which the lesion is to develop may have simply an hereditary or acquired hypersensitivity to estrogen and hence respond excessively to normal amounts. Predisposed smooth muscle cells may become fibroids under the influence of a quite normal ovarian function. If this were the case, however, the predisposition and not the hormone must be considered the essential cause of the tumor.

Three possible sources for an excessive supply or abnormal type of estrogenic hormone in the human organism may nevertheless be considered.

1. Origin from follicles: The cystic ovary has been implicated by clinicians and pathologists in a variety of lesions, including endometrial hyperplasia, endometriosis, fibromyoma and chronic cystic mastitis. In spite of this the functional significance of the cystic ovary is all but unknown. In some types the epithelium of the cysts is degenerate and the fluid contains little or no hormone. In others the granulosa and thecal cells are well preserved and the cyst fluid contains estrogen (Philipp,²⁰⁶ Moulouquet,¹⁸⁸ Metz,¹⁷⁹ Adair¹) and rarely an anterior pituitary-like hormone as well (Siegmond,²³⁰ Brindeau, Riehl, Hinglais and Hinglais,²⁵ von Probstner,²¹⁰ Mozzetti-Monterumici¹⁸⁹).

The cause of these functional cysts of the ovary is also little understood. There still exists a school believing that the cause is a local one in the form of a hyperemia or congestion resulting on the one hand in the speeding up of follicle ripening, and on the other in an eventual fibrosis which makes rupture of the follicle mechanically difficult. Both experimental and clinical evidence on the other hand point also to the anterior pituitary gland as a factor in at least certain types. Cystic conditions can be produced in the animal ovary by the injection of the anterior pituitary hormone or the implantation of the gland (Engle,⁷⁷ Selye and Collip²²⁵). Injection of the anterior pituitary-like hormone of pregnancy into women some days before an expected laparotomy has resulted in cystic and degenerative changes in the ovaries (Zondek,²⁷⁵ Mandelstamm and Tschalkowsky,¹⁷⁶ Geist,⁹⁷ Hamblen and Ross¹¹⁰). The small cysts discovered in the ovaries of the newborn have been explained as the result of stimulation by the placental hormone reaching the fetal circulation or of the infant's own pituitary activity (Spivack²³⁵). Finally cystic ovaries have been noted in patients suffering from various types of intracranial lesions in which functional disturbances of the anterior pituitary were probable (Cushing and Davidoff,⁶³ Kraus¹⁴³). The theca lutein cysts associated with hydatidiform mole and chorioepithelioma are probably also examples of effects of high concentrations of pregnancy hormone.

Thus it appears that the cystic ovary is a possible indicator of anterior pituitary activity, and a possible sign of abnormal ovarian function. Nothing could be more important in the elucidation of the lesions said to be due to an ovarian disturbance than a method of determining the functional significance of certain ovaries, particularly those with multiple small cysts.

2. Origin from ovarian tumors: The cases of granulosa cell tumor with endometrial hyperplasia give perfect examples of a demonstrable source and demonstrable effect of estrogenic substances. These cases are of course not common, but it is possible that small tumors or less organized cell collections similar in origin and in function to the granulosa cell tumors may more often be the source of hormone.

3. An extra-ovarian source: The origin of estrogenic substances outside of the ovary is easily demonstrable. First it is known that males excrete definite amounts of estrogenic substance and secondly it has been shown that women continue to have estrogenic material in the blood and urine after the menopause, after radiation of the pelvis, and even after surgical removal of the ovaries (Frank and others⁸⁵).

Recent work on the chemistry of the ovarian hormones has shown their relationship on the one hand to cholesterol and the bile acids (Rosenheim and King,²¹³ Wieland and Dane,²⁶⁰ Butenandt,⁴⁵ Dodds⁷⁰) and on the other hand to a series of derivatives of tar which are actively carcinogenic (Cook, Hewett and Hieger,⁵¹ Cook, Dodds, Hewett and Lawson⁴⁹). From these advances in the chemistry of these substances two theories deserve consideration: (1) Estrogenic substances may arise in association with the metabolism of cholesterol and the bile acids, quite out-

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and ovary was determined. These studies demonstrated displacement of the ovary cranially and caudally and rotation of the ovary on long axis. The ostium of the tube was noted projected at first over the upper pole of the ovary and subsequently over the uterine pole.

Suction of ova into the tubes, set up by cilia and also due to rhythmic contractions of the tube, is discussed.

The author notes that the ligaments of the human adnexa contain a great amount of smooth muscle and concludes that ova are transferred directly from the ruptured follicle to the tube in a manner similar to that noted in experimental animals.

S. J. SOULE.

Samuels, J.: *Early Diagnosis of Pregnancy*, München. med. Wchuschr. 84: 1323, 1937.

The writer presents a direct spectroscopic method of diagnosing early pregnancy. He employs an instrument, called a cycloscope (spectroreductometer), which determines the reduction of oxyhemoglobin, which in nonpregnant individuals takes about 145 seconds. Pregnancy is diagnosed when the cyclic variations which are observed in nonpregnant individuals are absent. He claims that the cycloscope will, in every case, diagnose a pregnancy seven or eight days after conception or twelve days before the time of the next menses.

The test is rapid and simple and can be carried out by any physician.

J. P. GREENHILL.

Patterson, Jocelyn: *The Chemical Diagnosis of Early Pregnancy*, Brit. M. J. 2: 522, 1937.

A biochemical test for the diagnosis of early pregnancy is described which is based upon bacterial splitting of oestriol glycuronide and the subsequent development of the oestriol color reaction with phenolsulphonic acid. Of 65 cases, in all except one, the results coincided with those of the Friedman reaction.

The advantages and disadvantages of the test as compared with other biologic tests are discussed.

F. L. ADAIR AND S. A. PEARL.

Schneider, Bernhard, and Cohen, Armand: *Nonspecificity of Gonadotropic Factor of Pregnancy Urine Intradermally*, J. A. M. A. 109: 115, 1937.

The results obtained with antuitrin-S, injected intradermally, in no way exhibit the reliability of this test as a means of diagnosing pregnancy or gynecologic disorders. One hundred eighteen tests were done on 95 females and 23 males. The observations made would indicate that 11 individuals were nonpregnant and 107 were pregnant. Actually, however, there were only 21 pregnancies.

GROVER LIESE.

Gill, A. Morton, and Howkins, John: *The Antuitrin S Intradermal Pregnancy Test*, Brit. M. J. 2: 1069, 1937.

The authors attempted to substantiate the favorable results reported by early investigators of the antuitrin-S intradermal pregnancy test. Male medical students, and pregnant and nonpregnant females were studied. The cutaneous reactions were read at one-half, one, and two hours. The results from antuitrin were so palpably inaccurate for the first 147 cases that the investigation was abandoned at that point.

Thinking that perhaps the foreign protein rather than the specific hormonal content accounted for some of the skin reactions, an additional 41 individuals were tested with inactivated antuitrin-S. The results from this group were as fallacious

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Selected Abstracts

Physiology of Pregnancy

Samuels, J.: An Exact Method of Determining Ovulation and Pregnancy, J. Obst. & Gynaec. Brit. Emp. 44: 1036, 1937.

The author discusses previous experimental work in which by means of an abdominal window he observed directly the tubes and ovaries of rabbits during various phases of the estrus cycle. He noted that the tubal fimbriae were dragged across the ovary to and fro. This phenomenon is explained by contraction of the smooth muscle and mesotubarium. The ovary was seen to shift its position cranially and caudally due to rhythmic contractions of the muscular ovarian ligament, rotating on the long axis so that its various surfaces faced the fimbriae and the ostium abdominale.

With the monkey a laparoscope was utilized during various phases of the cycle. During the interestrual phase the tube lay laterally convex, moderately twisted and bow-shaped so the pars ampullaris and pars isthmica approached each other and the infundibulum turned to face the ovary. Minor movements were observed by which the fimbriae were dragged to and fro across the ovary. The ovary was noted to be displaced cranially and caudally as well as rotatory. These phenomena are explained by the action of smooth muscle in the mesotubarium and ovarian ligament.

A series of observations in man are reported. At laparotomy for associated conditions the ovary was injected with a drop of lipiodol under the tunica albuginea at the upper and lower poles and in the free border prior to closing the abdomen.

Subsequently these patients were followed with serial roentgen films to ascertain the position of the opaque indicators and also to determine the reaction of the ovary to dye-filled tubes. These observations demonstrated a definite alteration in the position of the ovary, and in some cases the relative anatomic position of the tube

Kehrer believes that diabetes mellitus develops primarily after the puerperium and states that the disease is more common in parous than in nonparous women. He further believes that septic puerperal processes are not uncommonly followed by fibrous atrophy of the pituitary, thyroid, ovaries, and adrenals.

EUGENE S. AUER.

Celentano, Pasquale: The Proteolytic Ferments of the Hemocytes in Pregnancy, *Archivio di Ostetricio e Ginecologia* 41: 685, 1935.

The proteolytic ferments of the leucocytes were studied in 26 pregnant women. It was found that there was an increase in the tryptic power, and furthermore a peptic enzyme, not present in the normal woman, was noted. These findings can be explained by the presence in the blood of a greater amount of protein of alimentary origin not completely digested in the intestine.

J. M. PIERCE.

Fernandez-Ruiz, César: Calcium and Magnesium Balance During Pregnancy, *Med. ibera* 1: 102, 1936.

The author found that during pregnancy an increase in magnesium is accompanied by a reduction in calcium. He believes that magnesium has an inhibitory action upon the deposition of bone-forming substance.

F. L. ADAIR AND J. SUAREZ.

Effkemann, G.: Changes in Fat Metabolism Before the Onset of Labor in Normal Pregnancy, *Arch. f. gynäk.* 159: 718, 1935.

The author describes the incretory changes which take place in the pregnant woman just before labor sets in and gives his own findings regarding changes in fat metabolism during this period. He finds the fatty acid content of the blood during the several days preceding the onset of labor higher than it was during the second half of pregnancy. His values ranged from 700 to 850 mg. per 100 c.c. of blood. The acetone bodies were likewise increased during this period. The acetone values in pregnant women average 240 mg. and begin to increase about six days before labor sets in, finally reaching values of 640 mg. in the daily urine. The hypophyseal hormone regulating fat metabolism is also slightly increased during this time.

RALPH A. REIS.

Fronticelli, Enrico: The Maternal, Fetal and Placental Blood Urea Index, *Clin. obstet.* 14: 641, 1935.

From a study of the urea content of the blood of the mother, fetus and placenta, immediately after delivery, the author concludes that the maternal nitrogen content of the blood is lowered during labor; the fetal nitrogen content is independent of the maternal nitrogen content and is lowered a day or two after birth. The placental and fetal nitrogen contents are almost alike. The function of the placenta, in regard to the fetal nitrogen content, is like that of the kidneys, in the sense that it maintains the blood nitrogen index within physiologic limits and conveys urea to the maternal blood.

AUGUST F. DARO.

Traverso, G. L.: Study of Erythrocyte Volume During Pregnancy, *Folia Gynaec.-Demograph.* (Genova) 34: 449, 1937.

In a study of the blood of 322 pregnant women the author found that the red blood corpuscles obey the laws of hematic compensations. That is, the increase of volume of a single red corpuscle corresponds to the decrease of the number of elements in the unit of volume of blood and vice versa. Since his findings show a progressive decrease of volume of the single element from the beginning of pregnancy up to the fourth month with permanence of the minimum volume from the

as those obtained with active antuitrin-S. The authors concluded that this test for pregnancy, though enthusiastically acclaimed by some, has proved valueless in their hands.

F. L. ADAIR AND JOHN A. HAUGEN.

Abramson, Hurwitt, and Gerson: Relaxin in Human Serum as a Test of Pregnancy, *Surg. Gynec. Obst.* 65: 335, 1937.

A substance in the corpora lutea of sows and the serum of pregnant rabbits, which was capable of producing symphyseal relaxation in guinea pigs in normal or artificial estrus, was first described by Hisaw and named relaxin.

Although slight to moderate degrees of relaxation can be produced in guinea pigs by large doses of theelin, the separation is greatly increased by a small additional dose of relaxin. Pelvic relaxation in pregnant animals is therefore not solely a theelin effect.

A procedure has been developed for concentrating human blood serum taken from women in the first half of pregnancy which has acted on guinea pigs in a manner similar to that of relaxin. Symphyseal relaxation in guinea pigs in artificial estrus was produced by the sera of 15 consecutive women in the first half of pregnancy. The serum of 1 woman in the eighth month of pregnancy and that of 2 nonpregnant women and of 1 male were ineffective.

It is believed that pelvic relaxation during pregnancy is facilitated by, or at least in part is due to, the hormone relaxin in the human species as well as in many other mammalia. As a routine test of pregnancy this procedure is deemed impractical.

WM. C. HENSKE.

Crew, F. A. E.: The Aschheim-Zondek Test in the Puerperium, *Brit. M. J.* 1: 363, 1936.

There is no general agreement as to when, following pregnancy and normal parturition, the Aschheim-Zondek test first gives a permanent negative result. Aschheim and Zondek state that the reaction may disappear as early as five days after childbirth, and regularly ceases after eight days. Mazer and Edeiken believe that two weeks is the possible limit, while Hamburger states that the hormone content abruptly falls in the first twenty-four hours after delivery and in the succeeding twelve days gradually drops below any demonstrable level. Mack and Agnew found positive results two to seven days following parturition in four cases. Robson states the test is positive "about a week or ten days" after living products of conception are present.

The author followed a series of 50 cases daily and reports his results. Only 2 patients gave positive tests seventy-two hours after parturition and ninety-six hours after delivery all cases were negative. Five cases were negative seven hours after delivery. Out of these one gave a weekly positive test twenty-four hours after, and the other four continued consistently negative.

The conclusion, therefore, is that the Aschheim-Zondek test invariably yields a definite and presumably permanent negative result ninety-six hours after normal and complete parturition. The test may be adopted on the fifth day of the puerperium as a means of determining retained living products of conception.

F. L. ADAIR AND S. A. PEARL.

Kehrer, E.: Endocrine Syndrome During Pregnancy and After the Puerperium, *Ztschr. f. Geburtsh. u. Gynäk.* 110: 105, 1937.

The author states that there usually is a hypertrophy of most of the endocrine glands during pregnancy, more pronounced perhaps in the pituitary with the hypertrophy of eosinophilic cells which are the cause of the signs of acromegaly that are so frequently observed during the latter half of pregnancy. The increase in size of the pituitary body may indirectly result in diabetes insipidus. After the puerperium, symptoms of pituitary adiposity may appear associated with amenorrhea. Thyroid insufficiency may complicate the pituitary deficiency at a later date.

The authors studied the thyroid glands of a large number of pregnant animals. They believe that this gland has a wider range of physiologic variation than has been acknowledged heretofore. The evidence accumulated points toward a slight increase in activity of the gland during pregnancy, which is entirely physiologic in character. This increased activity in the animals was most pronounced in the earlier months of pregnancy.

To prove changes one must have positive knowledge of the gland before the onset of pregnancy as well as afterward. In this district 30 per cent of the young women have enlarged thyroid glands before pregnancy, which corresponds very closely to the number reported during pregnancy. Furthermore one must differentiate between enlargement due to lack of iodine and enlargement due to pregnancy.

H. CLOSE HESSELTINE.

Traut, Herbert F., and McLane, Charles M.: Physiological Changes in the Ureter Associated with Pregnancy, Surg. Gynec. Obst. 61: 65, 1936.

The normal ureter of the nonpregnant woman is possessed of rhythmic peristaltic activity which can be measured and recorded.

In the majority of 34 patients studied, this rhythmic peristaltic activity is definitely altered by pregnancy in varying degrees. There is a diminished amplitude of the peristaltic wave, commencing in the third month of pregnancy, but reaching its peak during the seventh and eighth months. After the fifth month the number of patients showing diminished ureteral response exceeds those showing normal activity. During the last month of pregnancy there seems to be a definite return of muscular irritability as expressed by the measurement of peristalsis and response to stimulation.

This diminished peristaltic activity of the ureters in pregnancy cannot be explained on a basis of passive dilatation. Dilatation of the ureters during pregnancy is probably in great part dependent upon the atony of the ureters due to some unexplained chemical factor.

WM. C. HENSKE.

Traut, McLane, and Kuder: Physiological Changes in the Ureter Associated with Pregnancy. The Relationship Between Atony and Dilatation of the Tract, Surg. Gynec. Obst. 64: 51, 1937.

New evidence is brought to light indicating that the physiologic dilatation of the ureter in pregnancy is not due to the weight of the pregnant uterus primarily, although this is undoubtedly a contributing factor. The characteristics of the ureteral atony are thought to be similar in many respects to that affecting the uterine musculature. It is suggested that the phenomena in the two organs may have a similar etiology which is unknown.

The ureteral dilatation is roughly proportional to the degree of atony and both appear and disappear at similar times with regard to the course of pregnancy.

Dilatation and atony appear in the third month and are progressive to the seventh month of pregnancy. During the last two months, there is a marked increase in motility, accompanied by a moderate decrease in the dimensions of the tract. Following delivery, atony is again marked until the third week, subsequent to which motility returns rapidly to normal levels, which are usually attained during the sixth or the seventh week post partum. Dilatation of the tract decreases progressively after delivery and reaches practically the normal values at the seventh week of the puerperium.

WM. C. HENSKE.

de Snoo, K.: The Drinking Child in Utero, Monatschr. f. Geburtsh. u. Gynäk. 105: 98, 1937.

De Snoo performed experiments whereby he sweetened liquor amnii to entice babies in utero to drink large amounts of liquor. He also attempted to treat babies in utero directly by introducing medication into the amniotic sac. Since 1922 he has

fourth to the seventh month, and furthermore show progressive increase during the eighth and ninth months, without having the said volume reach that of the normal isonumeric red corpuscles, the author suggests that pregnancy stimulates microcytic activity.

MARIO A. CASTALLO.

Landt and Benjamin: Cardiodynamic and Electrocardiographic Changes in Normal Pregnancy, Am. Heart J. 12: 592, 1936.

Observations were made on 19 normal pregnant women throughout the course of their pregnancy and puerperium. The study included correlation of clinical, cardiodynamic, and electrocardiographic changes. Final examination was made approximately two months after delivery. The study indicates that pregnancy definitely places a burden on the cardiocirculatory system. In the normal woman this burden can be compensated by calling on the reserve capacity of this system. The method of compensation is both mechanical and physiologic. The electrocardiographic changes during pregnancy may be interpreted definitely on the basis of mechanical shifting of the heart, usually expressed in a left axis deviation in the electrocardiogram. The normal woman who does not develop any untoward signs or symptoms during the course of pregnancy shows a normal clinical, cardiodynamic and electrocardiographic picture six to eight weeks after delivery.

J. P. GREENHILL.

Burwell, C. Sidney: The Placenta as a Modified Arteriovenous Fistula, Considered in Relation to the Circulatory Adjustments to Pregnancy, Am. J. M. Sc. 195: 7, 1938.

The demonstrated phenomena of the circulation in pregnant women plus the evidence offered by the structure of the placenta lead to the conclusion, that the changes in the circulation during pregnancy are in the main to be ascribed to two mechanisms: (1) Obstruction to venous return by the enlarged uterus; (2) an arteriovenous leak through the placenta.

J. THORNWELL WITHERSPOON.

Piccone, L.: The Larynx in Pregnancy, Folia Gynaec.-Demograph. (Genova) 31: 131, 1935.

The author refers to previous studies of this question. His histologic studies on dogs and rabbits demonstrated common changes in all the organs of the body and certain slighter modifications limited to special areas, particularly glottis and epiglottis.

In the larynx, can be observed new formation of blood vessels, a hyperemia of the vessels themselves, together with a more or less marked lymphatic infiltration. The connective tissue is found to be edematous with lymphatic spaces greatly dilated.

These changes were not found in the nonpregnant control animals nor in animals subjected to hormonal injections.

These processes, the author feels may explain the rapid progress of laryngeal tuberculous lesions during pregnancy.

MARIO A. CASTALLO.

Abbott, A. Clifford, and Prendergast, James: The Histology of the Thyroid Gland in Pregnancy, Canad. M. A. J. 34: 609, 1936.

The three principal beliefs regarding the thyroid gland in pregnancy are: (1) that the thyroid gland becomes hyperplastic during pregnancy, (2) that the thyroid gland becomes hypoplastic or colloid in nature during pregnancy, (3) that there is no change in the histology of the thyroid gland. In general, American observers favor the hyperplastic theory, while continental workers believe that there is no change or that the gland becomes colloid in nature. As yet, there is no definite proof of pathologic change.

operative measures, such as inductions of labor and cesarean sections. All operative procedures are associated with a certain risk.

It is important to evaluate carefully the past obstetric history. Antenatal care will contribute to the lowering of the maternal death rate especially when guided by sound judgment, and dexterity and patience in parturition.

H. CLOSE HESSELTINE.

Bak, M.: The "Cold Test" During Pregnancy, Labor and the Puerperium, *Monatschr. f. Geburtsh. u. Gynäk.* 105: 24, 1937.

During pregnancy, the "cold test" (dipping of hands into cold water) produces an average elevation in blood pressure of about 20 mm. Hg. Even among healthy gravidas there are variations in the reaction. In women who have a tendency to develop the toxemias of pregnancy and in those who have had such toxemias, there is a very rapid and pronounced rise in blood pressure, and this elevation is sustained for a longer time. In women who have the toxemias of pregnancy, the cold test produces only a slight increase in the blood pressure. It may remain constant or it may even fall. The results obtained with this test during pregnancy, labor and the puerperium do not vary from one another.

J. P. GREENHILL.

Evans, Arwyn: Variations of Weight During Pregnancy, *Brit. M. J.* 1: 157, 1937.

The variations in weight of 211 patients, 52 of whom developed toxemia, have been investigated and analyzed by the author.

The average gain of the toxemic patients was found to be definitely more than that of the normal patients. Moreover, a sudden abnormal increase in weight was of great value in foretelling a toxemia; 63 per cent of the patients who gained more than 8 pounds in one month became toxemic, whereas the incidence of toxemia in those patients with a normal monthly gain was only 0.9 per cent.

If a patient gained more than 5 pounds in a particular month it did not invariably signify that a toxemia would develop, but 98 per cent of the toxemic patients showed this abnormal gain.

This abnormal increase in weight appeared, on the average, one month before the albuminuria, and was as a rule an earlier sign than a raised blood pressure.

The type and duration of labor did not appear to be affected by increased weight of the mother. Loss of weight a few days before labor was noted in only 36 per cent of the cases.

It was concluded that systematic weighing of patients during the antenatal period is of definite value in foretelling, and perhaps avoiding, the toxemias of pregnancy.

The average increase in weight during pregnancy is 16 to 18 pounds, and the monthly gain during the second and third trimesters is normally between 2 and 4 pounds.

An increase of 5 pounds or more per month is suggestive of an impending toxemia, the probability of its occurrence varying directly with the amount of the sudden increase.

Every patient should be weighed regularly throughout pregnancy, and be instructed to consult her doctor if the monthly gain is 5 pounds or more.

F. L. ADAIR AND S. A. PEARL.

Wahl, F. A.: Are Children Larger and Does Pregnancy Last Longer Than Formerly? *Deutsche med. Wchnschr.* 63: 769, 1937.

Measurements on more than 6,000 premature newborn infants revealed the length-weight quotient averages 51.5 cm.: 3,400 gm. A comparison of these values with those formerly determined and accepted indicates that mature infants are longer as well as heavier than was formerly assumed. Regarding the duration of pregnancy, the author says that former studies in 4,000 cases, which have been corroborated by more recent studies in 5,000 cases, indicated that, counting from the last menstruation, pregnancy lasts from 284 to 285 days; that is, from four to

treated more than 20 babies in this way, and he is convinced the procedure has practical value. His first attempts were to reduce polyhydramnios by sweetening the liquor amnii with saccharin to make the baby swallow large amounts of fluid. By this means he succeeded in overcoming polyhydramnios, enabling women to carry their pregnancies to full term. In these cases the babies were somewhat edematous at birth and showed saccharin in the urine.

In some cases the author injected methylene blue into the amniotic sac. This dye was absorbed by the intestinal tract of the baby and eventually found its way into the mother's urine which stained blue. Since the membranes do not absorb methylene blue, we have here a means of determining whether or not a baby has swallowed water. The author found that the urine did not uniformly stain blue, but there were intervals when the urine was clear. The urine stained deepest when the child was most active. The author therefore believes that the child sleeps in utero for a few hours at a time and on awakening moves about and drinks water.

The procedure recommended by de Snoo can be used to determine whether or not a baby in utero is alive. There are two exceptions to this however. The first is the child who cannot drink, as in many cases of anencephalus and the second is the baby in whom the imbibed water cannot be absorbed, as in atresia of the esophagus and pylorus.

The author's experiments prove that excessive liquor does not come from the fetal kidneys but from the placenta and amniotic epithelium.

J. P. GREENHILL.

Sontag, L. W., and Wallace, R. F.: Changes in the Rate of the Human Fetal Heart in Response to Vibratory Stimuli, Am. J. Dis. Child. 51: 583, 1936.

That the human fetus is capable of perceiving sound vibrations has been shown by reports as the following: A case of Forbes and Forbes of a woman who while attending concerts noticed increased fetal movements whenever the audience applauded. Peiper reported increased fetal movements following certain sound stimuli. Ray observed fetal movements in response to the sound of two boards clapped together. Similar observations had previously been recorded by Sontag and Wallace.

In this new study the same authors investigated in a total of 217 experiments on 8 women in various stages of pregnancy the possible effect of vibratory stimuli on fetal heart rate. They found such an increase, averaging about 11 beats per minute, in response to vibratory stimuli applied to the mother's abdomen with a frequency of about 120 beats to the second. The rate of increase was the larger the nearer term the pregnancy was. They conclude that response to vibratory stimulation thus is expressed not only in increase of fetal movements but as well of fetal heart rate.

HUGO EHRENFEST.

Strachan, Gilbert I.: Some Problems in Antenatal Supervision, Lancet 2: 665, 1936.

Obviously antenatal care is to determine any abnormalities and to correct them. Even with the institution of this service the maternal mortality has not been appreciably altered. Pelvimetry has only a limited value due to the fact that soft tissue alters the size of the birth canal. The determination of the diagonal conjugate is inaccurate. The more important matter in borderline pelvis is the size of the baby in relation to the maternal passage and its presentation. Occipitoposterior positions may suggest disproportion. Trial labor will determine this more exactly.

One cannot predict in advance the position of the presenting part, the amount of molding, strength of uterine contractions or degree of joint relaxation. Breech presentation in the primigravida may become a difficult problem. External version may rectify the condition, yet this procedure may result in separation of the placenta.

Hemorrhages are usually unpreventable, but toxemias may be discovered early. A failure to decrease the maternal mortality rate may be the result of unnecessary

Unruptured follicles are red; black follicles of all sizes have no significance and must be disregarded. Corpora lutea visible to the naked eye do not develop within forty-eight hours, nor can they be seen with the low-power binocular microscope. In many cases the low-power microscope is necessary in order to reach a correct decision.

The common modification of the Friedman test is satisfactory, though the original Friedman technique gives better quantitative results. One injection of 10 c.c. of urine with examination in thirty-six hours is not nearly as successful as the double injection, and better results would be obtained with two injections and examination in forty-eight hours. Rabbits weighing more than three pounds will give better results than those weighing less, and three pounds is a safe minimum. It is safer not to use urines with a specific gravity of less than 1.008.

GROVER LIESE.

Thomson and Cohen: *Studies on the Circulation in Pregnancy*, Surg. Gynec. Obst. 66: 591, 1938.

Vital capacity and related observations on 31 normal pregnant women (21 primiparas, 10 multiparas) comprise the material for this report.

Since the vital capacity does not, as commonly supposed, decrease spontaneously during normal pregnancy, a significant decrease during pregnancy must be explained by some pathologic state.

The "dyspnea of pregnancy" depends largely on the ratio between vital capacity and pulmonary ventilation. A large increase in pulmonary ventilation with only a slight increase in vital capacity to accompany it, would lead to the development of dyspnea. This is precisely what happens in pregnancy. The pulmonary ventilation increases considerably, an average 57 per cent increase.

The irritability of the "respiratory center" is heightened. Finally it is reasonable to speculate that the altered lungs of pregnancy may, through the mechanism of reflex dyspnea from the congested lungs, lead to increased ventilation and dyspnea.

The vital capacity in normal pregnant women is within the limits set as normal for nonpregnant women. During the course of normal pregnancy, the observed vital capacity usually remains constant or shows a slight increase. The observed vital capacity decreases after delivery in most cases. There is an increase in the subcostal angle during pregnancy, with a post-partum decrease. The increase in vital capacity during pregnancy parallels closely the increase in subcostal angle value, as does the post-partum decrease. The change in vital capacity in pregnancy is associated with alterations in the size and shape of the chest. The increase in the observed vital capacity in pregnancy is not proportionately as great as the increase in body weight and approximate surface area. The vital capacity in the lying position during pregnancy is approximately 5 per cent less than in sitting and standing positions, but changes in a similar way. The vital capacity in the standing position during pregnancy is slightly higher than in the sitting position. Age and parity have no apparent effect on the vital capacity in pregnancy.

WILLIAM C. HENSKE.

Gerdes and Boyden: *The Rate of Emptying of the Human Gall Bladder in Pregnancy*, Surg. Gynec. Obst. 66: 145, 1938.

Detailed cholecystographic studies of 21 healthy gravid women, following intravenous administration of iso-iodikon, have shown that while the gallbladder could be visualized in 18 of them, 4 of the 5 that were tested both ante partum and post partum exhibited improved concentration of the dye six to eight weeks after parturition. This finding points to a gestational alteration in the concentrating power of the gallbladder wall.

The rate of emptying of the gallbladder, as testified by the modified Boyden meal, is not significantly different from the normal rate during the first three months of pregnancy, but in the second and third trimesters there is a marked retardation in flow, the mean discharge in 13 cases being only 52 per cent (at forty minutes post cibum) as against the normal nulligravida mean of approximately 73 per cent.

five days longer than was formerly assumed. He suggests that the comparatively greater length and weight of the newborn infant are due to the fact that gestation lasts longer than formerly. He also discusses the length of pregnancy with regard to the date of conception, pointing out that, on the basis of his own observations and of the results obtained by Knaus, Ogino, and others with regard to the term of ovulation, the average duration of pregnancy (counted from conception) is from 273 to 274 days. After directing attention to similar phenomena, such as the increase in the average height and in the life expectancy, the author cites several, particularly social-economic environmental, factors to which these changes may possibly be ascribed.

J. P. GREENHILL.

Rucker, P.: Effect of Diet on Outcome of Pregnancy, Kentucky M. J. 35: 329, 1937.

In the opinion of the writer, the Prochownik diet is a distinct help in the management of labor of a patient with a contracted pelvis. A patient on this diet has a tendency to go into labor prematurely, and the labor is distinctly shorter. Some 200 babies of mothers on a Prochownik diet were of average length but had less than average weight. There was no evidence of toxemia or kidney damage in any of the patients, and there was no indication of harm to the baby.

J. P. GREENHILL.

[It might prove interesting to add here the following data: When Prochownik, in 1889, first proposed a specific diet for patients with minor pelvic contractions he was not aware of the fact that similar suggestions had been made by several writers as early as the end of the eighteenth century. By the experience gained with *three* patients he felt justified in recommending for the last six weeks of pregnancy a diet poor in liquids and carbohydrates and rich in proteins, in general resembling the diet usually prescribed for diabetic patients. The results obtained in these three cases to him seemed most satisfactory. The three children showed no evidence of having been harmed by the changed and restricted food supply of their mothers, and exhibited all the characteristics of full maturity. They were of average length with normal skeletons, all bones apparently as hard as normally seen. Striking in some of these children was only the obvious deficiency in fat tissue.

Readily acknowledging that the head dimensions were found normal, the skull bones of normal hardness, Prochownik offered the following explanation for his observation, that in these three instances labors subsequent to the diet seemed easier in comparison with preceding ones: *A striking thinness and slackness of the skin covering the head, due to the absence of fat tissue, increases the mobility of the skull bones against each other, facilitates molding, and thus permits an unusual degree of compression of the head during labor.]*

HUGO EHRENFEST.

Murless and McLaughlin: Does Superfoetation Occur? Brit. M. J. 1: 1309, 1937.

The authors present the case of a multipara with a long and interesting obstetric history in whom six successive stillbirths were followed by the delivery of two full-term babies ninety-two days apart. The explanation suggested is superfetation.

Many similar cases are described in the old literature but none in recent years. The condition is rare but does occur. Some of the old literature is outlined in which evidence is presented that ovulation may occur during pregnancy; that cases of abortions of fetuses differing widely in size and development occur frequently; and that superfetation has been induced in animals.

F. L. ADAIR AND S. A. PEARL.

Kelly and Woods: A Quantitative Study of the Friedman Test for Pregnancy, J. A. M. A. 108: 615, 1937.

The presence of one or more *ruptured* follicles in one or both ovaries as well as the presence of several *unruptured hemorrhagic* follicles in both ovaries constitute a positive reaction for this test.

Central Association of Obstetricians and Gynecologists

The Tenth Annual Meeting of the Central Association of Obstetricians and Gynecologists will be held at the Hotel Radisson in Minneapolis on Thursday, Friday, and Saturday, October 6, 7, and 8, 1938, in connection with the Minnesota Society of Obstetrics and Gynecology. Dr. Jennings C. Litzenberg will be the honored speaker.

Washington Gynecological Society

At the Annual Meeting, held May 9, 1938, the following officers were elected:

<i>President:</i>	Joseph J. Mundell
<i>First Vice-President:</i>	Herbert P. Ramsey
<i>Second Vice-President:</i>	Richard L. Sylvester
<i>Treasurer:</i>	George Nordlinger
<i>Historian:</i>	John W. Warner
<i>Secretary:</i>	H. J. Russell McNitt
<i>Council:</i>	Howard F. Kane
	Leon A. Martel
	Albert E. Pagan
	William J. Stanton
	Jerome F. Crowley

International College of Surgeons

The Second National Assembly of the International College of Surgeons will be held in Philadelphia, Pa., with the headquarters at the Bellevue Stratford Hotel on October 13 and 14, 1938. All members of the medical profession of good standing are cordially invited to attend the scientific program and various clinics. There will be no registration fee.

Assembly of Laboratory Directors and Serologists

A meeting, under the auspices of the Committee on Evaluation of Serodiagnostic Tests for Syphilis, with Surgeon General Thomas Parran, Chairman, is scheduled for October 21 and 22, 1938, at Hot Springs National Park, Arkansas.

The aims and purposes of the assembly will be to consider means and methods to improve and to make more generally available the serologic tests, which are so important in syphilis control work. Tentative arrangements call for the presentation of the program in four sections.

The first section will consider the need for adherence to conventional technic in the routine performance of reliable serodiagnostic tests. This subject will be considered in papers by Drs. Harry Eagle, William A. Hinton, Reuben Kahn, Benjamin Kline, and John H. Kolmer, with special reference to the tests which each of these workers has described.

Need for training of laboratory personnel will be the subject of the second section. The qualifications and training for both laboratory directors and technicians will be presented in separate papers.

The third section will discuss the prosecution of the studies to evaluate the performance of serologic tests within the States. The efficiency of branch State laboratories and of municipal, hospital, and private laboratories cannot be studied on a national basis. The subject is much too large. Should this be made a function of the State or large municipal department of health? Actual experience with such studies in the States of Maryland and New Jersey and in the City of Cleveland will be described.

Even more significant is the comparison of the rate of emptying in the same individual before and after parturition. The mean discharge at forty minutes post cibum in 5 patients subjected to this test, was only 38 per cent during pregnancy as against 71 per cent, six to eight weeks post partum.

On the basis of Westphal's peptone and pilocarpine experiments with gravid women, this initial delay in the response to a motor meal is attributed to a hypertonic condition of the sphincter choledochus, i.e., to a physiologic dyskinesia reflecting the changed hormonal content of the organism in pregnancy. The evidence indicates that this delay is a lengthening of the normal "two-minute pause" that usually occurs immediately after the first rise in tonus of the gallbladder wall following ingestion of food.

The resulting biliary stasis accounts for the distended gallbladders found at term in 75 per cent of Potter's large number of cesarean sections and for the thick, tarry contents of gallbladders at term which are characterized by a low bile-salt (and a high cholesterol) concentration that is comparable only to that found in vesicles with a damaged wall. In conclusion, it is believed that the stasis of pregnancy sets the stage for the sequence of events which results in the greater incidence of gall stones among women that have borne children.

WILLIAM C. HENSKE.

Hirst, John Cooke, and Strousse, Flora: *The Origin of Emotional Factors in Normal Pregnant Women*, Am. J. M. Sc., 196: 98, 1938.

So-called "normal pregnant women" might well be highly abnormal, and even if they are not they are anxious to a degree beyond that of the so-called "normal" non-pregnant female. Types of anxiety are influenced by the social and economic group from which they are selected. In the group of 50 cases adequately followed up after childbirth, even though the economic situation was unchanged, there was a definite lessening of anxiety in 40 cases. The authors make a plea for at least one experienced dispensary staff attendant at each prenatal clinic, and for a note of the nervous status on each obstetric record. All women showing phobias or even marked anxiety during pregnancy should receive sympathetic encouragement by the chief of service, and if necessary, psychiatric advice. Among 100 presumably normal pregnant women 75 per cent showed anxiety related to economic stress; 7 per cent to their husbands, 10 per cent to other members of their families; while 16 per cent showed definite phobias concerned with fear of ill-health or death, or of the child being defective.

J. THORNWELL WITHERSPOON.

Items

Chicago Gynecological Society

The following officers were elected for the ensuing year:

<i>President:</i>	David A. Horner
<i>President-Elect:</i>	Julius E. Lackner
<i>Vice-President:</i>	Harold K. Gibson
<i>Secretary:</i>	Edward Allen
<i>Treasurer:</i>	George H. Gardner
<i>Pathologist:</i>	John I. Brewer
<i>Editor:</i>	William B. Serbin

THE PATIENT AND THE WEATHER. By William F. Peterson, M.D. Vol. IV. Part 3. Organic Disease—Surgical Problems. Edwards Brothers, Inc., Ann Arbor, Mich., 1938.

HEMORRHOIDS. By Marion C. Pruitt, M.D., Atlanta, Georgia. President, American Proctologic Society, Associate in Surgery, Emory University School of Medicine, etc. With 73 illustrations, including 7 in color, 170 pages. The C. V. Mosby Company, St. Louis, 1938.

SYMPTOMS OF VISCERAL DISEASE. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By Francis Marion Pottenger, M.D., Medical Director, Pottenger Sanatorium for Diseases of the Chest; Professor of Clinical Medicine, University of Southern California, etc. Fifth edition, with 87 text illustrations and 10 color plates, 442 pages. The C. V. Mosby Company, St. Louis, 1938.

ESSENTIALS OF OBSTETRICAL AND GYNECOLOGICAL PATHOLOGY, with Clinical Correlations. By Marion Douglass, M.D., Assistant Professor of Gynecology, Western Reserve University, and Robert L. Faulkner, Senior Clinical Instructor in Gynecology, Western Reserve University. With 148 illustrations, 187 pages. The C. V. Mosby Company, St. Louis, 1938.

SEX SATISFACTION AND HAPPY MARRIAGE. By the Reverend Alfred Henry Tyrer, Clergyman of the Protestant Episcopal (Anglican) Church. Foreword by Robert L. Dickinson, M.D., New York. Emerson Books, Inc., New York, 1938.

EAT AND KEEP FIT. Scientific Secrets of Diet. By Jacob Buckstein, M.D., Consulting Physician in Disease of the Stomach to Central Islip Hospital, etc. 128 pages. Emerson Books, Inc., New York, 1938.

TEXTBOOK OF CLINICAL PATHOLOGY. Edited by Roy R. Kracke, M.D., Professor of Pathology, Bacteriology and Laboratory Diagnosis, Emory University, etc. With the assistance of twelve outstanding contributors. Illustrated, 567 pages. William Wood & Company Division, Williams & Wilkins Company, Baltimore, 1938.

EL CICLO DE LA MUCOSA VAGINAL EN LA MUJER. Par Guillermo di Paola. Illustrated, 76 pages. Editor: El Ateneo, Buenos Aires, 1938.

THE ADRENAL CORTEX AND INTERSEXUALITY. By L. R. Broster, Clifford Allen, H. W. C. Vines, Jocelyn Patterson, Alan W. Greenwood, G. F. Marrian and G. C. Butler. With a foreword by Sir Walter Langdon-Brown. Illustrated, 245 pages. Chapman & Hall, Lim. London, 1938.

ANNUAL REPORT ON THE RESULTS OF RADIOTHERAPY IN CANCER OF THE CERVIX. First volume, collated in 1936. With appended Atlas. Edited by J. Heyman, Stockholm. Health Section of League of Nations. Geneva, 1937.

THE SINGLE WOMAN AND HER EMOTIONAL PROBLEMS. By Laura Hutton, physician, Tavistock Clinic, London. Second edition, 173 pages. William Wood and Co., Baltimore, 1937.

LEÇONS DU JEUDI SOIR A LA CLINIQUE TARNIER. Publiées sous la direction de A. Brindeau. Un volume, 318 pages, 66 figures. Vigot Frères, Paris, 1938.

LICÕES DE CLINICA OBSTETRICA. Par Clovis Correa da Costa, chefe do Serviço de Ginecologia do Hospital da Fundação Gaffrée-Guinle. Livraria Moura, Rio de Janeiro. 1938.

PROGRESSIVE RELAXATION. By Edmund Jacobson, A.M., Ph.D., M.D., Laboratory for Clinical Physiology, Chicago. 494 pages. The University of Chicago Press, Chicago, 1938.

The fourth section will consider the desirability of licensing or approving for the performance of serodiagnostic tests for syphilis, laboratories within the States by the respective State departments of health. This discussion will be conducted from the standpoint of the private laboratory director by Dr. Frederick H. Lamb of Davenport, Iowa. The health officer's side will be presented by Dr. A. Wadsworth, State Department of Health, Albany, N. Y.

An additional feature of the meeting will be an actual demonstration of the performance of the Eagle, Hinton, Kahn, Kline, and Kolmer tests by the originators of these procedures.

Those interested in obtaining further information should write to the Surgeon General, U. S. Public Health Service, Washington, D. C.

American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants by the American Board of Obstetrics and Gynecology, will be held in various cities of the United States and Canada on Saturday, November 5, 1938. Last day for applying is September 5.

The next general examination for all candidates (Groups A and B) will be held in St. Louis, Missouri, in June, 1939, immediately prior to the American Medical Association meeting.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania. Applications for these examinations must be filed in the Secretary's Office not later than sixty days prior to the scheduled dates of examination.

Books Received

MEN PAST FORTY. By A. F. Niemoeller, A.B., M.A., B.S. Illustrated, 154 pages. Harvest House, New York, 1938.

SYPHILIS, GONORRHEA, AND THE PUBLIC HEALTH. By Nels A. Nelson, Director, Division Genitoinfectious Diseases, Massachusetts Department of Public Health, and Gladys L. Crain, R. N., Epidemiologist, Division of Genitoinfectious Diseases, Massachusetts Department of Public Health. The Macmillan Company, New York, 1938.

MANAGEMENT OF THE SICK INFANT AND CHILD. By Langley Porter, Dean, University of California Medical School, and Professor of Medicine, etc., and William E. Carter, Director, University of California Hospital, Out-Patient Department, etc. Fifth revised edition, illustrated, 874 pages. The C. V. Mosby Company, St. Louis, 1938.

THE TREATMENT OF CLINICAL AND LABORATORY DATA. An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By Donald Mainland, Professor of Anatomy, Dalhousie University, Halifax, Nova Scotia, Canada. With 23 text figures, 340 pages. Oliver and Boyd, Edinburgh, 1938.

THE HEART IN PREGNANCY. By Julius Jensen, Assistant Professor of Clinical Medicine, Washington University School of Medicine, etc. 371 pages. The C. V. Mosby Company, St. Louis, 1938.

TWENTY-EIGHT YEARS OF STERILIZATION IN CALIFORNIA. By Paul Popenoe, Sc.D., and E. S. Gosney, B.S., LL.B. Pasadena, 1938.

sult that an animal was available in which fetuses within the uterus could be observed at full term, or at stages of postmaturity corresponding in development to newborn rabbits of one, two, or three days.

In the course of the experiments various anesthetics were used in order to permit exposure of the uterus. Occasionally, as the depth of anesthesia was diminished, a few irregular respiratory movements of the fetuses were noticed. These gasps tended to confuse the results of the experiments with stimulant drugs. It was decided to eliminate general anesthetic agents entirely. Accordingly, section of the lumbar spinal cord was done to produce loss of sensation over the abdominal region to be incised for laparotomy.

The first experiment carried out with this new technique, namely, the inhibition of labor and the elimination of anesthetics, disclosed the errors of experimental methods heretofore used, and revealed the intrauterine origin of respiration (Snyder and Rosenfeld, 1937).¹

Fetuses within the uterus were breathing actively. Rhythmical excursions of the chest wall and diaphragm continued throughout periods of observation lasting many hours. Through the thin uterine wall of the rabbit we could distinguish unmistakably that the movements were respiratory. Similar findings were obtained in the cat and guinea pig.

Observations were next made upon women. Spontaneous fetal movements of regular rhythm and of a distinctive pattern characteristic of fetal respiration were seen to be transmitted through the abdominal wall, and motion picture records of them were obtained (Snyder and Rosenfeld, 1937).²

Up to the present time asphyxia of the newborn has been approached by the clinician and the physiologist from a standpoint which has regarded the problem to be a matter of the sudden initiation of activity in a previously dormant system. In recent years the solution of the problem has been sought in terms of possible causes of the first breath of the newborn (Barcroft);³ search has been directed toward discovery of some mechanism which suddenly comes into operation at the time of birth.

Recognition of the origin of respiratory movements early in embryonic life necessitates revision of previous views. Inquiry must be directed to the determination of factors which may arrest activity rather than to those which might initiate a new process. With regard to the causes of intrauterine respiratory failure it may be pointed out that in rabbit fetuses showing regular respiratory movements, apnea may be induced of three different types, namely, (1) anoxemic; (2) acapnic; (3) anesthetic.

Prevention of asphyxia of the newborn, therefore, centers in the period preceding birth. It involves the recognition and control of factors which cause fetal anoxemia, and suggests caution in the selection and dosage of anesthetic and hypnotic agents.

Certain anatomic abnormalities of the lungs which are observed at the time of birth, namely, atelectasis and pneumonia, may be traced to pathologic complications of normal intrauterine respiration. The entrance of amniotic fluid into the alveoli of the lung is not a pathologic complication of labor, but can be clearly demonstrated to be a normal

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Original Communications

FETAL RESPIRATION IN RELATION TO ATELECTASIS AND INTRAUTERINE PNEUMONIA*

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BALTIMORE, MD.

(From The Johns Hopkins University)

THE present experiments represent an attempt to throw light upon the nature of certain familiar injuries of the respiratory system which are evident in the newborn at the time of birth. They include: (1) Asphyxia neonatorum, or failure of the nervous mechanism which controls respiration; (2) atelectasis, or incomplete dilatation of the alveoli of the lungs; and (3) pneumonia of the stillborn.

Since these injuries are present at the time of birth, it is evident that they must originate during intrauterine life. How these complications involving the respiratory system can occur while the fetus is still within the uterus requires explanation. In order to trace the origin of these abnormalities, it is essential to determine the normal state of activity of the respiratory system of the fetus before birth.

I. PHYSIOLOGIC FACTORS IN THE CONTROL OF INTRAUTERINE RESPIRATION

The work began with an attempt to resuscitate asphyxiated babies by the injection of respiratory stimulants, and later was carried over to laboratory animals. Injection of various respiratory stimulants directly into rabbit fetuses within the uterus was tried in an effort to overcome the fetal apnea. No success was met. We were surprised for two reasons at this failure to arouse the fetus from a state of apnea. First, various traumatic factors associated with delivery had been eliminated, since the fetus was studied before the onset of labor; and second, in the rabbits studied, prolongation of pregnancy had been accomplished by the injection of pregnancy urine extract with the re-

*Presented at a meeting of the Obstetrical Society of Philadelphia, November 4, 1937.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

With the onset of breathing of air there is a striking increase in the dilatation of the alveoli which is clearly evident within one minute following delivery (Fig. 2). In a littermate which survived delivery for two days, the dilatation of the alveoli is increased still further.

Investigation has also been extended to the human being to include observations upon the structure of the lungs before and after birth. In human fetuses obtained before the breathing of air, the lungs were not completely collapsed but showed well-formed alveoli (Fig. 3). It was definitely known that no air had been breathed, since the full-term fetus was obtained at autopsy, being removed from an intact amniotic sac two hours following death of the mother from eclampsia. The cervix was not dilated and the membranes were unruptured. The alveoli are patent and the degree of dilatation reveals the effectiveness of the tidal movements of fluid throughout the respiratory tract. It is evident that respiratory movements within the uterus exhibit a function which is retained throughout postnatal life, namely, the capacity to expand the alveoli.

Microscopic examination of the human fetal lung gives additional evidence that the alveoli are not empty before birth but that amniotic

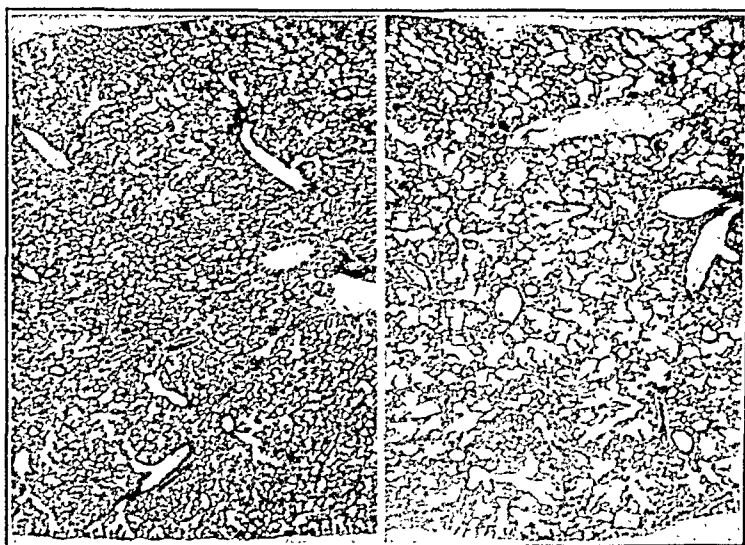


Fig. 1.

Fig. 2.

Fig. 1.—Normal rabbit lung before birth. The fetus was showing regular respiratory movements within the uterus at the time of sacrifice. $\times 20$.

Fig. 2.—Increase in size of the alveoli one minute after delivery and the onset of the breathing of air. The animal is a littermate of the fetus in Fig. 1. The rapid expansion of alveoli at birth prevents drowning of the newborn. The alveolar surface now obstructed by amniotic fluid thus becomes relatively greatly reduced. $\times 20$.

fluid fills the lung (Fig. 4). Cells and debris, characteristic of amniotic fluid are readily identified in the alveoli and bronchi of fetuses which had died before removal from the amniotic sac.

Another problem arises at this point. If the alveoli are filled with amniotic fluid at the time of birth, why is the newborn not drowned? A clue is afforded by microscopic examination of the lungs shortly after delivery when breathing of air has just begun.

In the lung of a child which had died eight and one-half hours after delivery (Fig. 6), the dilatation of the alveoli is in striking contrast to that observed in lungs obtained before the breathing of air had begun (Fig. 5). In the human being, as well as in the rabbit, it is

consequence of fetal respiration. The presence within the lung of amniotic fluid and a tidal exchange of this fluid between the alveoli and the amniotic sac has been proved by experiment. India ink injected into the amniotic sacs of littermates enters the alveoli or the lungs of fetuses which are breathing, but in apneic fetuses fails to enter the lungs (Snyder and Rosenfeld).⁴

The rate of exchange of fluid between the lungs and the amniotic sac has also been determined. In breathing fetuses particles of ink enter the lungs within a minute after injection, blackening of the lungs being easily evident without magnification.

Additional evidence showing that the alveoli contain amniotic fluid before birth is afforded by the regular occurrence of cellular debris of amniotic fluid in the lungs.

In the light of these findings it is evident that breathing of abnormal amniotic fluid containing debris of excessive amount or abnormal type may result in injury of the lungs before birth. Obstruction of bronchioles during intrauterine life may lead to incomplete dilatation of alveoli, or atelectasis. Contamination of the amniotic fluid by irritant substances, e.g. meconium, or bacteria may cause inflammatory changes of the lungs before birth, and result in the death of the fetus with intrauterine pneumonia.

The occurrence of fetal respiratory movements throughout a large part of intrauterine life and the effectiveness of these movements in maintaining a tidal flow of amniotic fluid between the interior of the lungs and the amniotic sac lead to the conclusion that intrauterine respiratory movements are essential for the development of a normal lung.

II. DILATATION OF THE PULMONARY ALVEOLI BEFORE AND AFTER BIRTH

In order to compare the state of dilatation of the alveoli in lungs obtained before air is breathed with those of animals which had breathed air for various intervals following delivery, rabbits were prepared according to the method previously described for the observation of intrauterine respiration. Fetuses were removed from one horn of the uterus and after breathing of air for periods of one minute or longer, the trachea was clamped. The animal was dropped into formalin. A half-hour later the chest wall was incised to facilitate fixation; two days later the lungs were removed for histologic examination. As a control, fetuses of the opposite horn were dropped into formalin without removal from the uterus, after the trachea had been clamped through the intact uterine wall. Intrauterine respiration was occurring in many of these fetuses at the moment when the clamp was applied.

Results of a typical experiment are illustrated by lungs obtained from three littermates, sacrificed at twenty-nine days, which is the beginning of the period of viability. In the control fetus which had never breathed air, the lung is not collapsed but the alveoli are patent and well developed (Fig. 1). The degree of dilatation of the alveoli reveals the influence of intrauterine respiratory movements.

during intrauterine life the alveolar septa become thin and the alveoli are partly dilated; in the second stage, occurring after the breathing of air, there is a rapid increase in alveolar expansion. Current views regarding atelectasis of the newborn and its pathogenesis have been reviewed and criticized recently by Farber and Wilson (1933).^{5, 6}

The foregoing attempt to determine the normal degree of dilatation of the alveoli during intrauterine life on the one hand, and on the other to distinguish that stage of expansion which characterizes early postnatal life, may clarify the nature of atelectasis. It seems evident that atelectasis may arise during intrauterine life as a consequence of obstruction of the normal tidal flow of amniotic fluid in the respiratory tract. In case obstruction occurs at the time of delivery, there will be failure of alveolar expansion beyond the stage normally present within the uterus. In establishing criteria for the recognition of atelectasis during early postnatal life it may be pointed out that the increase

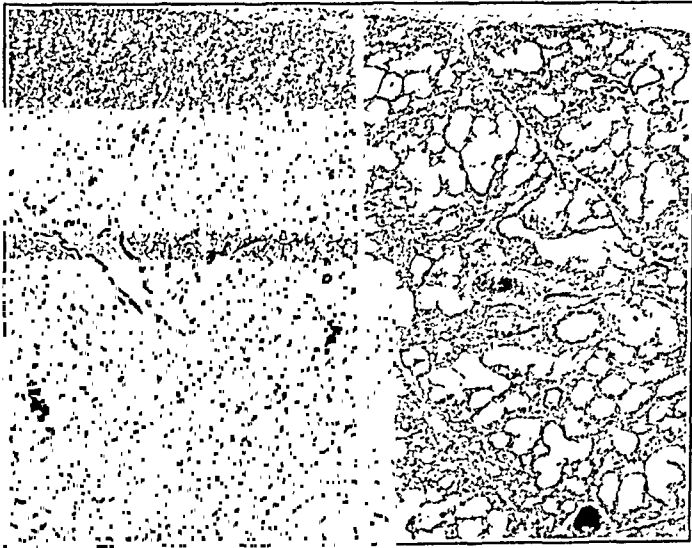


Fig. 5.

Fig. 6.

Fig. 5.—Lung of child before the breathing of air. The alveoli are well formed, showing that respiratory movements serve to expand the alveoli before birth as well as afterwards. The baby was stillborn following obstruction of the umbilical circulation during labor at term. $\times 20$.

Fig. 6.—Lung of child after breathing of air for eight and one-half hours, showing great increase in size of the alveoli. The baby cried at once following delivery by forceps at term but respiration ceased eight and one-half hours later. Autopsy showed intracranial hemorrhage and rupture of the tentorium. $\times 20$.

in expansion following the breathing of air is not uniform throughout all of the alveoli (Fig. 6). Widely dilated alveoli are seen adjacent to areas in which expansion of alveoli has not yet exceeded the stage characteristic of intrauterine life.

CONCLUSIONS

1. The lungs are not collapsed before birth, but the alveoli are well formed and partly dilated, being filled with amniotic fluid.

2. Breathing of air instead of fluid results in a rapid increase in the dilatation of the alveoli.

evident that, although the lungs contain amniotic fluid at the time of birth, the elasticity of the alveolar walls permits an increase in size of the alveoli of such magnitude that the surface area now obstructed by fluid becomes relatively greatly reduced.

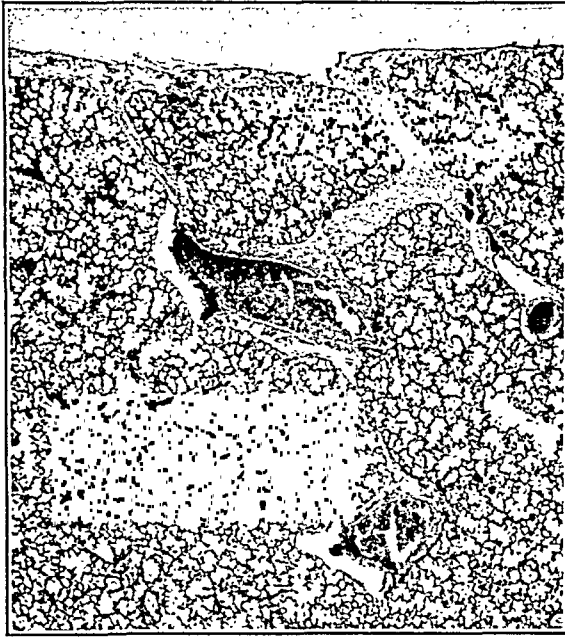


Fig. 3.—Normal human lung before birth. The alveoli are not collapsed, but are distended with amniotic fluid as a result of intrauterine respiratory movements. No air was breathed, since the full-term fetus was removed at autopsy from the intact amniotic sac, two hours following death of the mother from eclampsia. $\times 20$.

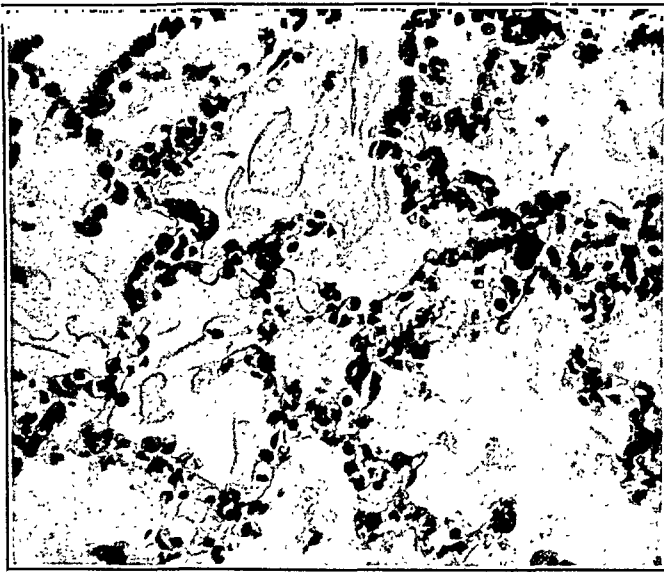


Fig. 4.—Alveoli of normal human lung before birth containing cellular debris of amniotic fluid. Same section as Fig. 3. $\times 350$.

In brief, a comparison of the structure of the lungs before and after birth shows that there is a gradual preparation for the sudden transition at birth from placental to pulmonary ventilation. Two stages in the expansion of the alveoli are clearly revealed: in the first stage, occurring

slowly; cyclopropane more rapidly, and ethylene and nitrous oxide more quickly than the other three. The elimination time, of course, is graded as it exists under average conditions, for with any given anesthetic it will vary with both the length of time and the depth of administration.

TABLE I. ACTION OF CERTAIN ANESTHETICS AND ANALGESICS

SCALE OF VALUES ++++ +++ ++ +	DEPRESSING EFFECT ON RESPIRATION	ELIMINATION TIME	O ₂ CONTENT AVERAGE CONDITIONS	POTENCY WITHOUT O ₂ WANT	EARLY RESPIRA- TORY STIMULATING EFFECT	CO ₂ CONTENT OF BLOOD	PRELIMINARY SEDATIVES	
							NON-VOLATILE AGENTS (THERAPEUTIC DOSES)	DEPRESSION RESPIRATORY CENTER
(C ₂ H ₅) ₂ O*	+++	+++++	++	+++++	+++++	-	Morphine sulphate	+++++
CHCl ₃ *	+++++	+++++	++	+++++	+	+++++	Barbiturates	+ to +++
(C ₂ H ₅) ₂ O*	+++	++	++	+++++	+++++	-	Scopolamine	0
C ₂ H ₄ †	+ or +++	++	+ or ++	++	++	+ to +++	Atropine	Stimu- lating
C ₃ H ₆ §	+++++	+++	+++++	+++++	0	+++++		
N ₂ O†	0‡	+	+	+	++	+ to +++		

*Open drop method administration.

†Semiclosed method administration.

‡Without sustained anoxemia.

§Closed c.c. absorption.

The oxygen content of the absorbed mixture under average conditions is somewhat dependent on the method of administration. With ether, chloroform, and ethyl chloride, when administered by the open drop method, some of the oxygen in the air will be displaced by the vapor of the anesthetic. Consequently, the customary 20 per cent is thereby somewhat reduced. The mucus produced by the irritant action of these agents also interferes with absorption which further decreases the intake of oxygen. With nitrous oxide and ethylene, the oxygen content of inspired mixtures is likely to be further decreased because of the relatively feeble nature of these agents. With cyclopropane the oxygen content is, of course, very high, as already explained.

The carbon dioxide content of the maternal blood has a relationship to the probable necessity of resuscitating the newborn. With an agent that markedly stimulates respiratory function, and with no provision for re-breathing, the carbon dioxide will, to a large extent, be eliminated. This occurs with ethyl ether and divinyl ether. Chloroform is a definite depressant to respiration, and therefore the carbon dioxide content of the blood will be high. With nitrous oxide and oxygen, the CO₂ of the blood depends largely on the amount of re-breathing instituted. With cyclopropane, which has no early respiratory stimulating effect, the carbon dioxide content of the blood is believed to be at a high level.

Among the nonvolatile sedative agents morphine sulphate has of course the greatest respiratory depressing effect. The barbiturates may be graded from 1 to 3. Scopolamine stimulates metabolism, and therefore the respiratory center, but this action is counteracted by its cortical depressant quality allaying emotional activity. Atropine stimulates the respiratory center to a certain slight extent, and probably also affects respiration directly through the mechanism of stimulating metabolism.

From the above description we learn that nitrous oxide is well adapted to obstetric anesthesia and analgesia if sufficient oxygen can be administered with it. Continuous care is, however, indicated to prevent anoxemia and anoxia. Cyclopropane is a depressant, but its elimination time is rapid and the high oxygen content administered with it is favorable. Ethyl ether is not quite so favorable, largely because of its slow elimination time.

3. The newborn is not drowned although the lungs are filled with amniotic fluid at the time of birth. Adequate aeration is promptly provided, since the elasticity of the alveolar walls permits an increase in size of the alveoli of such magnitude that the surface area now obstructed by fluid becomes relatively greatly reduced.

4. Breathing of abnormal amniotic fluid containing debris which obstructs the respiratory passages may result in injury of the lungs before birth and cause atelectasis. Bacterial contamination of amniotic fluid may result in intrauterine pneumonia.

REFERENCES

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DISCUSSION

DR. RALPH M. TYSON.—Dr. Snyder has shown us that the respiratory system functions before birth. Our problem as obstetricians and pediatricians is now to assist this system to carry on while the great changes in environment are occurring. Heretofore we have been accustomed to regard the problem simply as one of helping to initiate respiratory function after birth has occurred.

In a study of deaths over a seven-year period, we have found that early placental separation, placenta previa, abnormal cord conditions, and unknown causes of asphyxia, caused 14.4 per cent of the total deaths. If we were to add the deaths caused by cerebral trauma and atelectasis, newborn deaths due to asphyxia would reach 20 per cent. In addition many newborn babies recover from asphyxia, the cause of which in many instances is only a guess. These figures give a small idea of how important is this problem of respiration in the newborn.

Neonatal statistics are not of much help as given at present. The international list groups too many conditions under the heading "other diseases peculiar to early infancy." Asphyxia deserves separate mention and some steps should be taken to secure more detailed information on the part it plays in newborn mortality. A commission similar to the one on maternal mortality might be a good way to help solve this important problem.

DR. HENRY S. RUTH.—Since Dr. Snyder has mentioned the depressing action of certain anesthetic and analgesic drugs I would like to compare their characteristics which affect the maternal respiratory function, and therefore the respiratory activity in the newborn.

In the accompanying table I have listed only the agents commonly employed namely ethyl ether, chloroform, divinyl ether, cyclopropane and nitrous oxide. The characteristics about which we have definite information have been graded for each of these various agents on a sliding scale, 5 being the maximum response, and 1 the minimal response.

The most important information we should know about an agent is in regard to its depressing action on respiratory function. All the inhalation agents, with the exception of cyclopropane, produce a primary stimulation with a subsequent depression of respiration in the deeper stages of anesthesia. With ether and chloroform, on-coming depression occurs at the lower level of the second plane of the third stage of anesthesia. Cyclopropane, of course, is more depressing than ethyl ether, but its depressant effect is overcome to a large extent by the large volume of oxygen with which it is administered. Neither nitrous oxide or ethylene are in themselves depressing to respirations, but when accompanied by varying degrees of oxygen deprivation, corresponding degrees of respiratory depression are present. The duration of this depression of respiration is to a certain extent proportional to the elimination time of the agent. Ethyl ether and chloroform are eliminated

VISCERAL ALLERGY

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ALLERGY is a new science with unlimited possibilities. It may be of interest to abstract the first paragraph of a previous article to convey a broader concept of this difficult subject. The local and general manifestations of allergy are due to a local or general hypersensitivity to certain provocative substances, allergens, which either gain entry into the circulation by absorption through the alimentary tract, or by bacterial invasion, or by hypodermic injections; or they may act locally by contact, inhalation or any other mode of approach. The presence of an allergen either in the circulation, or by contact, in sensitive individuals, produces in the sensitive tissues certain protective antibodies, or antigens, which are liberated by these cells when the allergen invades their domain, and the resultant is a form of irritation expressed either as an extravasation or a spasm. The extravasation is due to definite changes in the capillary lining epithelium, and the spasm, it is thought, is due to irritation of the neuromuscular mechanism. These antibodies are called allergins. They are a protective device. The results in the sentient patient are protean in their symptomatology. The cells or organ affected determine, to a great extent, the nature of the symptoms. In the nose, the common manifestation is hay fever, or hemorrhages due to plasma, or cellular extravasations, respectively; asthma, due to involuntary muscular spasm and extravasations; urticaria, due to focal skin dystrophies; local edemas, due to subcutaneous outpourings; eczema and prurigo, due to disturbance of nerve nutrition; and disturbances of the genital cycles, due to spasm or derangement of the normal secretions. These are the commonly recognized manifestations. But there is no organ or system of the body which may not be the seat of allergic symptoms. It was shown, in a previous work, that the sex organs are commonly affected; that the migraine is an expression of brain allergy, and cases of spreading paralysis and coma were quoted, of undoubted allergic origin.

It is proposed to detail the cases in which unusual and startling trains of symptoms arise out of involvement of specific organs in allergic states, producing conditions closely simulating the well-recognized organic diseases. These will be dealt with in the following order: Intestinal, hepatic, peritoneal, cardiac, muscular, and cerebral.

Intestinal Allergy.—In a paper entitled "Mucous Colitis"¹ Goodall named allergy as one of the frequent causes of colitis. Further observation has confirmed this opinion beyond refutation. The condition may be a more or less permanent, chronic state, or it may be periodic in its

I would like to ask Dr. Snyder about the results of spinal anesthesia on intra-uterine respiratory movements and more about his experience with the barbiturates. I would like to ask how long he believes the intrauterine respiratory movements may be abolished by either anoxemia or anesthetic action, and still allow the fetus to be delivered viable.

Finally, since it has been our clinical impression that when cyclopropane has been administered for longer than fifteen to twenty minutes before delivery, there may be some difficulty in resuscitating the baby. I should like to know whether Dr. Snyder has administered it for more than fifteen minutes, and if so, whether or not there was ultimately produced an absence of these intrauterine respiratory movements.

DR. PENDLETON TOMPKINS.—We know that the total alveolar surface of the lungs is very large, and now Dr. Snyder has shown that before birth the alveoli are filled with amniotic fluid. It is therefore quite possible that an important fluid exchange, through transudation, occurs in the fetal lung. If such transudation can be shown to occur we may be able to explain certain cases of hydramnios or oligohydramnios. It is noteworthy that oligohydramnios has been noted in association with congenital stenosis of the trachea. Is this oligohydramnios the result of interference with fluid exchange through the lower respiratory tract?

DR. SNYDER (closing).—To explain the asphyxia associated with cesarean section under local anesthesia, or following spinal anesthesia, one might speculate as follows: Of the three types of fetal respiratory failure which were observed experimentally, namely, anesthetic, acapnic, anoxemic, one can rule out the first and second, leaving only anoxemia to be considered. The oxygen supply of the fetus may be diminished by impairment of the uterine circulation resulting from increased tonus of the uterine muscle. This effect becomes more marked as term is approached, since at this time the uterus responds more readily to stimuli, like exposure to air in the course of cesarean section, spinal anesthesia, oxytocic drugs.

Dr. Ruth asked how long after the circulation has been interrupted is it possible for a fetus to be born alive. We have done the following experiment. The entire litter of a rabbit at full term was obtained within the unopened uterus after sacrifice of the maternal animal and prompt extirpation of the intact reproductive tract. At various intervals fetuses were removed from the uterus and their ability to survive was noted. If removal to the air was delayed longer than fifteen minutes, the animals did not survive. Injury may be evident much sooner, and they may start to breathe but eventually succumb. Obviously this simple experiment does not settle the matter in the case of the human being.

With regard to the duration of narcosis in relation to the condition of the fetus at delivery, a large problem is presented. The matter of dosage arises and quantitative studies become necessary. We have merely tried to illustrate the qualitative aspect, namely, that the effect upon the fetus may differ strikingly from that upon the mother, following administration of numerous anesthetic and hypnotic agents. With cyclopropane the mother was deeply anesthetized, showing no corneal reflex for fifteen minutes at least, and yet the fetuses were breathing at a rapid, uniform rate. The opposite was true with pentobarbital, for with this drug fetal respiration was depressed or abolished before the maternal animal gave evidence of analgesia. Obviously, the fetus has a special physiology.

In connection with the question of the absorption of amniotic fluid by the fetal lung and the relation of hydramnios to fetal respiration, it is interesting to note that amniotic fluid is greatly reduced invariably in the rabbit as term is approached.

Regarding the removal of debris from the upper respiratory tract in resuscitation, one may stop to reconsider how much fluid the child can tolerate in the respiratory tract. The baby seems to have greater resources in taking care of fluid than we had surmised. Of course, amniotic fluid differs widely among individuals with respect to the amount and type of debris. One child is covered with a thick vernix caseosa while another is clean. Injury of the fetal lung results from breathing of abnormal amniotic fluid.

symptoms simulating gastric ulcer without hematemesis or the acute local tenderness, torpitude and flushing of the face after meals, palpitation and profound muscular and mental lassitude.

Hepatic Allergy.—Probably the most interesting type of spastic allergy is that which affects the bile passages, simulating hepatic colic and probably pancreatic regurgitation. These cases are moderately common. They have come under observation in the last year. The symptoms are those of hepatic colic. The pain is right-sided, referred to the breast, shoulder and back; occasionally (in one case) the pain had the distribution also of involvement of the pancreas, in that the pain radiated also distinctly to the left of the mid-epigastric line. The history suggests gallstones so closely that all the patients were operated upon for this diagnosis, without finding stones at operation or in skiagraphs. The history of one of these cases will do more to clarify this syndrome than any other enumeration of findings. The patient, a physician's wife, mother of three children, had five distinct and severe attacks characteristic of hepatic colic. X-rays were negative. Tipp test negative. But owing to their characteristic onsets and the severity of the symptoms, non-opaque gallstones became the final diagnosis. Operation revealed a perfectly healthy gall bladder and bile passages. The gall bladder was removed. Patient made an uneventful recovery. Three months later she had a severe recurrence, and six months later another. She then came under the writers' care for a menstrual disturbance of allergic origin. She gave a familial history replete with allergic manifestations. Her husband, the doctor, is also allergic, all her children are allergic. She herself had a minus 18 basal rate, and was devoid of gastric free hydrochloric acid. She had most distressing attacks of migraine. After being under observation, but before the diagnosis was made, she had two severe colic attacks. The second lasted almost three hours. In the attack, three-fourths of a grain of morphine only aggravated the symptoms. Morphine, it is interesting to note, raises the intrabiliary pressure. She now learned that these attacks invariably followed the use of compound tablets of aspirin, phenacetin, caffeine and codeine, which she took for her migraine and facial neuralgia. Since this determination, she has been wholly free from biliary attacks. Since being placed upon XXX minims of hydrochloric acid and 4 gr. of thyroid (Burroughs Wellcome) t.i.d.p.c., she is no longer appreciably allergic, being free from migraine and eschewing aspirin. It may be interpolated that aspirin is a very common allergen in susceptible patients.

Two other cases gave a history somewhat analogous. A fourth came into the surgical wards of St. Mary's Hospital and under the care of the surgical resident, Dr. MacCormick, who has had an extensive training in allergy at the Children's Memorial Hospital. X-ray and other tests were negative. Amyl nitrate and later adrenalin gave immediate and complete relief. Later it was found that the allergen was a food product. Its deprivation prevented a recurrence. In all these cases the condition seems to point to a spasm of the sphincter

manifestations, just as allergic states, as described and accentuated in a previous paper on allergy of the pelvis.² It may be added that the symptoms may be fixed in one part of the bowel, or may shift, affecting now one section of the colon, now another, and it may be further stated that the condition may be spastic or hypersecretive. The dominant symptom in the majority of cases is not acute pain, but a burning sensation. At times the pain is quite severe, occasionally crampy. There is generally tenderness over the ascending or descending colon. Backache is an invariable accompaniment. Constipation is the rule. The stools are small in the spastic type, large and covered with inspissated or glary mucus in the hypersecretive type. In this respect, mucous colitis of allergic origin does not differ from colitis from other causative agents. The pain or tenderness may be fixed over the cecal region, thereby resembling appendicitis or pyelitis; or a pendulous cecum may closely resemble right tuboovarian trouble. If the pain is permanently fixed at the hepatic flexure, cholecystitis may be suspected. When the transverse colon is affected, the symptoms may cause one to suspect gastric disease; and involvement of the splenic flexure may give the patient severe precordial pain, with a fixed idea that she is suffering from cardiac disease. Sigmoid involvement closely resembles the ovarian diseases, or may cause one to suspect diverticulitis, or pyelitis. Not infrequently an extension of the process to involve the rectum, causes tenesmus and exacerbation of any hemorrhoidal symptoms. The fact that the symptoms most frequently are not fixed, but pass from one colic area to another, almost at once leads one to suspect the correct cause. Palpation of the colon reveals general or local tenderness over the colonic area. The colon may be distended, or more frequently, present the hardness of a hawser. Constipation is the rule, with occasional bouts of bowel hyperactivity. There is always improvement after such a development. Upon awakening, there is a general abdominal soreness, and upon rising, backache and occasional articular rigidity.

A painstaking history, both personal and familial as to allergic susceptibilities, will greatly help in determining the proper cause. Alternating periods of recovery and recrudescence characterize the majority of cases. Patients are generally much more uncomfortable at the before or during the menstrual epoch.

Referred gastric symptoms are not uncommon. These are generally of the nature of nausea and eructations several hours after meals, or tremendous bloating.

Direct gastric symptoms are very varied, and may simulate organic gastric diseases so closely as to defy clinical differentiation. It is only by a process of exclusion, by tests of gastric function, which is not disturbed in allergic diseases, and by a suggestive personal and familial history of allergic manifestations, that the true nature of the dysfunction may be opined. In infancy, one of the commonest manifestations is pylorospasm, and regurgitation. In childhood, incipient hunger, followed after a small quantity of food, by an anorexia; in adult life,

ized to any special part. Especially prone to this local manifestation are the Fallopian tubes at the fimbriated ends. (Fig. 1.) In the cases where the peritoneum, visceral and parietal, is involved, the edema is variable in quantity, in one case presenting a truly water-logged condition (Figs. 2, 3, and 4). In another case described by a colleague, the peritoneum was like a soaked sponge. Under these circumstances, the peritoneum, being indifferently securely attached to its underlying



Fig. 2.—Normal peritoneum.

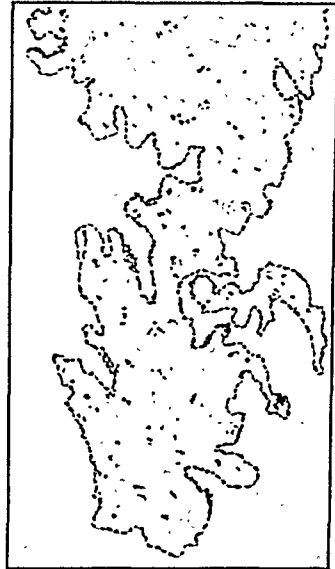


Fig. 3.—Slight peritoneal edema.

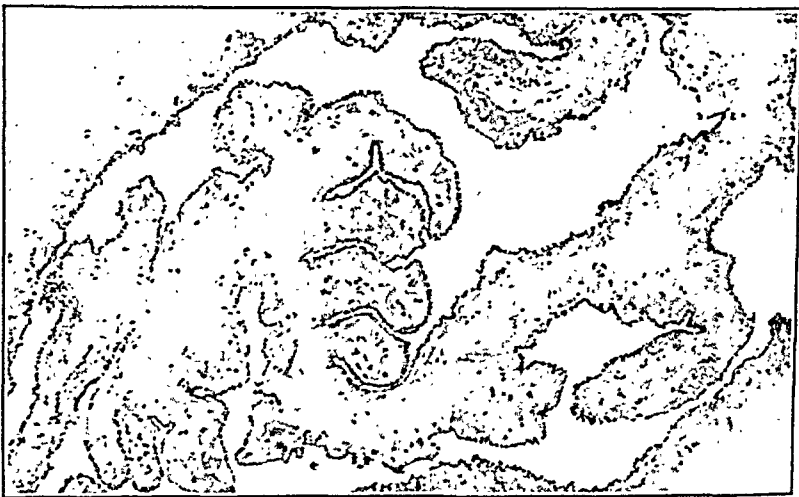


Fig. 4.—Allergic edema of the peritoneum, showing coagulum and liquid spaces.

structures, is thrown into numerous edematous convolutions which are covered by a single layer of flattened cells. Drawings of these demonstrate this condition very clearly. In other instances, the sections show the extravasated lymph in the widely dilated lymph spaces of the Fallopian fimbriae. In one case, a child of 7 years, very allergic, the peritoneum was as though it had been infiltrated everywhere by a syringe.

of Odie, and an elevation of intrabiliary pressure. Corroborative proof of this was found in the exacerbation of the condition by the use of morphine and its immediate relief by the antispasmodics, and by making the patient nonallergic, either by correcting the existing endocrine dysfunction, or by finding the causative allergen which disposes to allergic susceptibility. It was clearly pointed out in the previous paper, quoted above, that endocrine dysfunction often becomes the exciting factor in predisposed individuals, and the correction of the endocrine dyscrasia removes the susceptibility to allergens. It was also pointed out that the allergic state is familial or acquired, and is, in these cases, the constant subsoil which comes to the surface when the general health is lowered by disease or deranged function. Nothing in the human metabolism is left to hazard, each function being under the control of another function and it, in turn, under another. The final arbiters are the endocrines. Dysfunctions of these are the



Fig. 1.—Coagulated and liquid edema of the fimbriae. The empty spaces and dilated subfimbrial lymph channels were originally filled with liquid lymph. Coagulation has occurred only at the periphery.

necessary precursors of metabolic upsets. Under these dysfunctions of malnutrition of cell and body generally, familial, or acquired, allergic susceptibility may become a dominant factor in diseased states.

In the patient who had severe pain referred also to the left side, the inference was drawn that the intrabiliary pressure caused a back pressure along the duct of Wirsung into the head of the pancreas, thereby causing acute edematous pancreatitis, a condition so clearly described by Dr. Edward Archibald in "Acute Edema of the Pancreas" (*Ann. Surg.* November, 1929).

Allergy of the Peritoneum.—There are a few of these cases that are of minor degree. In a previous paper allergy of the pelvic cavity was fully described, especially when combined with pelvic inflammatory disease. However, allergy of the peritoneum may be general, without other signs of local disease, or the allergic extravasation may be local-

many spasms of a similar nature in other parts of the body, especially in the abdominal wall, intestines and uterus, are frequently complained of without ever a thought being given as to their true character. These are extremely common, and of unusual interest. They tend to recur in the same spot, when that area has once shown its susceptibility to its pregnancy change of environment. The muscles of the loins are particularly prone to this type of spasm, but any musculature may be involved. In two cases, the clinical interest is great, owing to the doubt which attended the cases until the proper diagnosis was established.

The first was a multipara, 38 years of age. Ten days before an anticipated delivery, she was seized with an excruciating pain in the right loin. Upon examination, there was no marked tenderness, slight rigidity, but the subjective symptom was intense. Morphine, $\frac{1}{4}$ gr., did not relieve at all, nor did a repeated dose effect any appreciable change. The pain gradually subsided, leaving a very marked soreness. Patient described it as a cramp. There had been no gastrointestinal disturbance, and a catheter specimen proved negative. The pain and soreness gradually wore off. A week later, I sectioned her and carefully examined all the organs of the right abdomen, without finding anything that offered an explanation. However, when coming out of the anesthetic, the patient again awoke to this fearful pain, which again was similarly localized, and would not respond to morphine. Suddenly its true character was defined, and the patient was given almost magical relief, by the administration of adrenalin.

In another somewhat similar case, the spasm of the oblique muscle could be distinctly felt. It was promptly relieved by adrenalin. Such abdominal spasms in the majority of pregnancies fortunately are of short duration, and do not require treatment. But it is well to be au fait as to their true character, and to the knowledge that they can be relieved, but not by morphine or other narcotics; antispasmodics would be a more logical procedure.

Cerebral Allergy.—Last, the effects of allergy upon the central and peripheral nervous system. In the previously quoted work on allergy, the authors described a case of allergic paresis during pregnancy, due to excessive extravasation of fluid from the choroid plexus. It is now well recognized that allergic edema of the brain is extremely common, rarely expressing itself in convulsions, but commonly in migraine, hemiparesis, hemifacial spasm, neuritis, papillary and conjunctival edema.

DIAGNOSIS

The diagnosis will rest upon the history. A meticulously careful inquiry into the personal and family history for some of the stigmas of allergy is one of the most important preliminary steps. The presence or absence of hay fever, asthma, bronchitis, eczema, prurigo, local edemas, acute poisoning by certain food producing vomiting bouts, neuralgias, and migraine, especially at the time of menstruation should be noted. These should be followed by a careful physical examination, including all the sense extension means to exclude organic disease. The basal metabolic rate should be established, and when normal, if the clinical picture of allergy is convincing, the thyroid therapeutic test will frequently prove that the metabolic estimation is wrong. The writers invariably add 10 to a minus reading and subtract 10 from a plus,

Cardiac Allergy.—This condition can be diagnosed only by the history of allergy, symptoms, and recovery under appropriate treatment. The cardiac symptoms may vary from precordial pain to acute pseudo-anginal attacks with a residual of pain that may last for twenty-four hours or more. Several of these cases have come under observation in women of allergic traditions, in whom appropriate treatment has immediately relieved the spasm, and removal of the offending agent, or a correction of the defective metabolism, has led to permanent relief. It is thought by general pathologists that many of the cases of cardiac death, without demonstrated coronary disease, and more especially in children, are probably allergic in character. In Goodall's paper on the toxicity of colitis, cardiac distress and fear of impending death are fully described.

How frequently one finds among physicians and others, signs of acute and chronic cardiac distress due to the allergic cardiac effect of a focus of infection, the removal of which gives almost immediate release from both fear and pain. Mention need hardly be made of the pulmonary complications of allergy: asthma, bronchitis, pulmonary and laryngeal edema, and lingual and oral swelling.

An obstetric patient was admitted to the private ward, in what proved to be false labor. For economic reasons, a therapeutic induction was attempted with castor oil and pituitrin, beginning with 2 minims and increasing 1 minim every half hour until a dose of 7 minims was reached. It proved ineffectual. She returned to the hospital ten days later in true labor. When about fully dilated, with membranes ruptured, labor pains ceased, and the resident later gave her 3 minims of pituitrin. Within one-fourth of an hour the patient was cyanotic, her lips were twice their natural size, the tongue was swollen twice its normal dimensions, the face was edematous, there was air hunger due to laryngeal edema, and both lungs were filled with moist, diffuse râles. The condition was suddenly critical for both mother and child. Oxygen and helium were used with good effect, and after the administration of 5 minims of adrenalin, the patient quickly recovered. Her temperature, meanwhile, shot up to 104° F., and the pulse was over 140, and the blood pressure rose rapidly from 110 to 150.

In another case the patient, a graduate of the Montreal Homoeopathic Hospital, who had known that she was allergic to certain drugs, was given a hypodermic of morphine on her second day post partum. Within an hour, her face was swollen almost beyond recognition. The conjunctivae were so edematous that they hung in wrinkles. The tongue was half as large again as normal. Dyspnea supervened, and her temperature rose to 105° F., with a severe chill. Adrenalin quickly controlled the discomfort, and in twenty-four hours the patient was back to a quasinormal state.

Muscular Allergy.—Allergic muscular dystrophies are very common. One has but to recall the muscular spasm of asthma, to realize what a profound and persistent effect this may produce. But one finds muscular spasm of an allergic nature under many and varied pathologic states. The writers wish to draw attention to the muscular spasms of pregnancy, which are an expression of a toxicity-producing allergic spasm. The percentage of women who suffer from these painful spasms of the legs, thighs, and feet, is very high. The spasm is acute for a time, frequently leaving a soreness which may last some hours, even days. These are so common as to be regarded as something to be expected and endured. They are an expression of toxicity, and

The chronic cases, frequently allergic to many things, are the most deserving of our keenest study. They are highly susceptible cases, in which the hereditary influence is usually pronounced, and in which the hereditary subsoil is constantly, slightly, or much exposed.

They have a multiplicity of symptoms, affecting now one system, now another, dyspnea, tachycardia, arrhythmia, migraine, neuritides, gastric disturbances, colitis, spastic dysmenorrhea, menorrhagia and metrorrhagia, articular pains, etc. They constitute the great majority of our so-called neurasthenics. The contributing cause for aggravation may be economic, moral, mental, or emotional. They are not the self-pitying type, but, being conscious of their unwonted irritability, generally state that they are sorry for their husband or their children.

Frequently a change of scene, and a freedom from household cares, bring about almost magical changes. Other cases will frequently tax one's ingenuity, as well as one's patience, to the utmost limit. When improvement is brought about, it is usually temporary. Relapses are frequent and discouraging.

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WEIGHT CHANGES AND TOXEMIA OF LATE PREGNANCY*

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IN 1916 Zangemeister suggested observations on the weight changes of pregnant women for the detection, through large increases, of latent, occult, or preclinical edema, which he believed to be a sign of incipient toxemia of pregnancy. Since that time there have appeared a number of articles which have largely supported Zangemeister's recommendation. Some have even gone so far as to suggest regular weighing as not only highly valuable in predicting toxemia but also as a reliable means for the actual diagnosis of the established disease. A critical study of these articles shows that, with few exceptions, there is little more than authority of other authors or clinical impression to justify the views expressed. Where statistical evidence has been presented, it is frequently unconvincing or questionable because of insufficient numbers, lack of comparison with normal cases, or other reasons.

A previous study by us² presented, among other data, evidence against too great enthusiasm regarding the value of weighing for the early diagnosis of toxemia. Although excessive weight gains did precede the signs (hypertension and albuminuria) of frank toxemia in about

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thereby getting, it is thought, a fairer record of actual states by allowing for the nervous excitation of a first test. Allergics are notably hypothyroids, and a large number of them are achlorhydrics, so that before and after meals gastric free acidity test is essential, unless one applies the therapeutic test. Anemias are frequently profound and a distinct shift to the right, especially due to eosinophiles, is not uncommonly found, particularly during an attack. A blood sugar estimate must never be overlooked.

One of the worst cases of flaming vulvitis was encountered recently, in which the urine, on repeated examination by her physician, which had always been negative, showed blood sugar of only 98 m.g. before meals and after eating testmeal record of 119 m.g. Insomnia from the pruritus was almost dementing. She responded promptly to 5 unit doses of insulin, and was free from symptoms, but not of local discoloration, in five days.

TREATMENT

It will be found that a large percentage of allergies are facultative, conscious of discomfort only when the general health has sunk below the reserve of a gland, or of any system. In these it is but necessary to build them up so that they are again within their reserve, to bring about a clinical submergence of the allergic state. It cannot be too emphatically stated that these temporary allergic states, frequently accompanied by the most distressing symptoms, are due to a vitiation of function, brought about by a great diversity of activating causes, and it requires but the removal or correction of this cause, or causes, to submerge again the constant factor of hereditary allergic susceptibility. Nor can it be too strongly emphasized that no function of the body is left to hazard. Each and every function, no matter how insignificant, is under control. This control is generally vested in the endocrines, or in katalytic substances, the reduction or absence of which precipitates a vitiation and a consequent poisoning of the system, so that the lowered nutrition which follows, permits an emergence of the hereditary taint. In the vast majority of instances, it is but necessary to correct the dominant defect to re-cover the hereditary subsoil. Thyroid is the dominant endocrine dysfunction in these cases, and fortunately it is almost always a deficiency disease, so that supplemental administration of the extract becomes a simple procedure. Whether this is merely an accidental association, it is impossible to state with any degree of assurance, but the association of the two conditions is so common, beyond any possibility of explanation by the law of chance, that there would seem to be a decided interdependence, as cause and effect, or due to a common cause. However, the establishment of these associated defects gives one a ready means of treatment, by thyroid and hydrochloric acid. The allergic response is usually prompt and complete.

Glycemia should be excluded or, if present, treated appropriately. Anemias should be overcome. Parasitic intestinal diseases should be studied. Everything should be investigated to find a vitiating cause which did not exist when the patient was formerly nonallergic.

Of the 100 toxemia patients, 69 were primiparas. In 24 there had previously been one, and in 7, two or more term or premature deliveries. Determination of the types of toxemia offered the usual difficulties, but from the excellent records, not only for the present but also in many for past or subsequent pregnancies, it appeared that 55 had so-called "low reserve kidney," 20 chronic nephritis, 17 pre-eclamptic toxemia (pre-eclampsia), and 8 eclampsia.

The average gain in weight for the 100 toxemia patients during the last four lunar months of pregnancy was 17 pounds as compared to 15.7 pounds for the normals. In Table I the average gains during each observation period are given for the toxemia patients and for the normal patients from the previous report. Naturally, toward the latter part of pregnancy the averages were obtained from a diminishing number due to premature deliveries, though even at term there were 47 weights on toxemia patients.

TABLE I. AVERAGE WEIGHT GAIN IN POUNDS

WEEK	24-28	28-32	32-34	34-36	36-38	38-40	TOTAL
100 Toxemia	4.3	4.8	3.0	2.3	1.4	1.2	17.0
624 Normal	4.4	3.9	2.0	2.1	2.0	1.3	15.7

Since the foregoing figures run somewhat contrary to the usual opinion when they indicate only moderate increase in weight gain for toxemia, we considered the possibility that single or even several excessive gains occurring at different times among the patients might be concealed or masked, so to speak, in the averages. Consequently, each patient's record was examined for excessive weight gain at the above designated observation periods. Inasmuch as our previous study (confirmed by McIlroy and Rodway, and others) demonstrated many deviations from the averages even in normal patients, we selected twice the average (or more) as a practical figure to indicate excessive weight gain. Comparison was made with Table V of our previous paper, thus taking into consideration the factors of age and parity. This showed that 61 of the 100 toxemia patients had excessive weight gains to this extent at one or more times after the beginning of the seventh lunar month. The remainder of the cases, or the substantial number of 39, had no excessive gain at any time. Indeed, it is interesting to note in view of Zangemeister's observations on "hydrops gravidarum" that seven of these patients did not at any single observation period show a gain above the averages. Moreover, the average increase in weight during the last four lunar months for the group of 39 without excessive gain was only 11.6 pounds as opposed to the normal average of 15.7 pounds.

In order to investigate the possible variation in severity of toxemia in relation to the presence or absence of excessive gain, the disease was classified as mild when the highest systolic blood pressure was below 150 mm. of mercury; moderate with blood pressure of 150 or above but below 170; and severe if 170 or above. True eclampsias were classified as "severe" regardless of height of blood pressure. The percentage incidences of these grades of severity among the 61 with excessive gain were: mild, 19.7; moderate, 49.2; and severe, 31.1 (including 6 eclamp-

40 per cent, similar gains occurred at some time in approximately the same proportion of our normal patients. In the remainder of the patients with toxemia, excessive gains were noted for the first time coincident with or well after the onset of the disease, or not at all. These findings were so contrary to our expectations (based on the literature and our own clinical impressions) that, striking as were the results, we considered the possibility of error due to the small number (39) of toxemia cases studied. Consequently, we have assembled 61 additional cases to make a series of 100. Fifty of these occurred in our practices, while the remainder were obtained from the records of Drs. George Kamperman, Ward Seeley, and Harold Henderson whose kind permission and cooperation we wish to acknowledge.

In this series of 100 we included only patients with unquestionable toxemia as shown by systolic blood pressure of at least 140 mm. of mercury plus definite albuminuria. We eliminated all patients with multiple pregnancy and those with any disease or condition which could be expected to affect the weight. Furthermore, these were private patients of the white race, native born for the most part, and with no economic necessity for limitation of diet. Only patients who were weighed regularly up to term or within a few days of premature delivery were included. Also, in order to insure as high a degree of accuracy as possible, a clear and definite history of the last menstrual period was considered essential. Our calculations were made from weights taken at the twenty-fourth, twenty-eighth, thirty-second, thirty-fourth, thirty-sixth, thirty-eighth, and (in 47 cases) fortieth weeks.

The selection of case records conforming to the above criteria permitted a fair comparison with the series of normal patients in our former report. The fact that Cummings from the same region and with a similar type of patients obtained averages almost identical with the normals in our previous study supported our confidence in the reliability of those figures. With this exception, we have avoided weight for weight comparisons with series of other authors, though general trends and conclusions have been noted. We considered this to be a precaution in the interests of accuracy since the types of patients in various series differ so greatly. Certainly, for a number of reasons, private patients cannot be fairly contrasted with clinic patients. Furthermore, it is quite possible that factors such as race, nationality, and even locality are of importance in affecting weight gain.

Our former study, though showing numerous unexplained and often extreme deviations from the averages, indicated that age had definite influence on weight changes. Parity was also of some importance, but body build (or height-weight ratio) much less so. Consequently, as information regarding age and parity was available for the 100 toxemia patients, allowance for these factors was made in certain of the calculations by comparing each abnormal case to the averages for the corresponding age and parity group of normals. Actually, however, this precaution had no great effect on the final results.

of the disease. It *coincided* with hypertension, albuminuria, or both 15 times, and it *followed* the appearance of these signs in 9. To obtain a complete picture, we must consider the whole group, including the 39 without excessive gains at any time. In Table III it is seen that besides the 37 in which excessive weight increase appeared first, the earliest evidence of toxemia was: hypertension, 22; hypertension and albuminuria, 18; excessive weight gain with hypertension and sometimes also albuminuria, 15; and albuminuria alone, 8. (As there were 100 patients in the group, percentages are of course the same as the case incidences.)

TABLE III. EARLIEST SIGNS OF TOXEMIA IN 100 CASES

SIGNS:	EXCESSIVE WEIGHT GAIN	HYPERTENSION	HYPERTENSION AND ALBUMINURIA	EXCESSIVE WEIGHT GAIN HYPERTENSION ALBUMINURIA	ALBUMINURIA
Number and percentage	37	22	18	15	8

Calculations from Table III apparently suggest that as the earliest indication of toxemia, excessive weight gain (52 cases), either alone or combined with other signs, approximates in value the appearance of hypertension (55 cases), albuminuria being of much less importance. Furthermore, since excessive weight increase preceded other signs in 37 per cent of the toxemias, it might seem of real value in discovering the disease in its incipency. A practical difficulty in application, however, is found in the fact, frequently ignored, that a large proportion of normal patients also have these large gains. In our previous report 280 of 624 normals (about 45 per cent) showed this excessive gain one or more times during the last four lunar months and were delivered at term without any evidence of toxemia. Consequently, our figures indicate that acceptance of excessive gain as reliable evidence of incipient toxemia necessitates subjecting approximately one-half of all pregnant women to treatment. A comment⁷ on our previous study that, "It is easy to tell if the gain in weight is due to water or fat," is not in accord with our experience, or apparently that of others, since the water retention we are here largely concerned with is hidden or occult and not demonstrable as edema. Incidentally, it may be mentioned that, in addition to large weight gains, we also see various degrees of edema in a fair number of otherwise normal patients, sometimes without much weight increase. Furthermore, it is most common and most marked in warm weather when toxemia is said to occur least often. Finally, a considerable number of patients with definite, and even severe, toxemia show no edema, either demonstrable or occult.

Those who, in spite of the foregoing data, may be convinced of the advisability of prophylactic treatment in patients with excessive weight

sias). For the 39 without excessive gains the percentages were not greatly different, being respectively 20.5, 41.0, and 38.5 (2 eclampsias). (See Table II.)

TABLE II. SHOWING THE PERCENTAGE INCIDENCE OF MILD, MODERATE, AND SEVERE TOXEMIA WITH AND WITHOUT EXCESSIVE WEIGHT GAINS DURING THE LAST FOUR MONTHS OF PREGNANCY

	MILD TOXEMIA	MODERATE TOXEMIA	SEVERE TOXEMIA
With excessive gains (61 cases)	19.7	49.2	31.1
Without excessive gains (39 cases)	20.5	41.0	38.5

The relationship of the type of toxemia to excessive weight gains was inconclusive due to the small numbers of cases, though perhaps of some significance. The 55 “low reserve kidney” cases showed about the same ratio as the whole series, namely, 33 (60 per cent) with excessive gain at one or more observations, and 22 without. Nephritis complicating pregnancy was evenly divided, 10 with and 10 without. The 17 with pre-eclamptic toxemia (pre-eclampsia) showed 12 with and 5 without excessive gain. Six of the 8 eclampsias were associated with excessive increase.

As stated in the opening paragraph, regular weighing as a part of pre-natal care has been advised repeatedly as an efficient means of predicting and thus forestalling the onset of toxemia, the idea being that definite signs of the disease are preceded in a large proportion of the cases by excessive weight gains due to occult edema. Most worthy of consideration in this regard is the recent study of Evans who not only agreed with this advice but even suggested the procedure as an excellent means of detecting fully developed toxemia, apparently considering it more useful than blood pressure observations and urinalysis. He stated that 82 per cent of toxemias could be discovered by weighing alone. It may not be amiss to point out that Evans’ conclusions were based on the records of only 211 patients (apparently a series of consecutive cases) of whom the surprising number of 52 were classified as toxemia. Fifteen of these showed no albuminuria and therefore did not meet the usual criteria for toxemia of pregnancy. However, even if these patently doubtful cases are eliminated, there still remain 37, an unusual toxemia incidence of 17.5 per cent, or 1 in 6 pregnancies. The incidence at Harper Hospital (private and clinic) during the last four years has been 4.4 per cent, including some patients who, but for the toxemia, would have been delivered elsewhere. McIlroy and Rodway go so far as to state that they have prevented many cases of toxemia by alertness in respect to large gains and the institution of prophylactic treatment. Though not denying this as a possibility, we believe their statement would be more credible if they could show an untreated control series for comparison, especially since another section of their paper confirms our previous study in showing that there are many patients who have excessive weight gains and yet go to term without toxemia.

Examination of our 100 toxemia cases showed that among the 61 with excessive gain there were 37 in which this *preceded* definite signs

group (with preceding gains well above the average), toxemia 24.6—normal 42.5. (See Table IV.) It is apparent, then, that a sudden large increase in body weight is somewhat more common among toxemia patients than among normals, though it is far from the rule.

In presenting the foregoing observations, we do not wish to be understood as condemning routine prenatal weighing as useless. Indeed, it is of value other than in its possible relationship to toxemia. However, so far as toxemia is concerned, we do feel that the significance of excessive weight gain has apparently been misunderstood or greatly overrated. Our data show it to be far from reliable as a sign of impending toxemia. And, though we will agree that routine weighing may be considered as a possible adjunct in detecting the actual disease, it can by no means replace established procedures such as routine blood pressure determinations and urinalyses.

SUMMARY

A series of 100 private patients with definite toxemia of late pregnancy had an average gain in weight of 17 pounds during the last four lunar months of pregnancy, as compared to 15.7 pounds for normals. Sixty-one of these 100 toxemia patients gained at least twice the normal averages at one or more observation periods during this time, while 39 at no time showed such excessive gains. The presence or absence of excessive weight increases bore little or no relationship to the severity or to the type of the toxemia. In 37 patients, excessive weight gain preceded definite signs of toxemia, but in the remaining 63 it appeared along with or after these signs, or not at all. Moreover, it was also present in about 45 per cent of the normals. Sudden or abrupt weight increase was somewhat more frequent with toxemia than among normal patients but was far from the rule. The occurrence of excessive weight gains in pregnancy would appear to be of doubtful significance in predicting impending toxemia and of secondary value, at most, in the diagnosis of the actual disease.

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gains will find a confusing and often contradictory list of recommended procedures, such as: general restriction of caloric intake; full feeding in malnourished patients; specific limitation of proteins, carbohydrates, fats, or salt; a diet of milk only; endocrine gland products; restriction of water intake; forcing of large quantities of fluids; strict bed rest; and increased bodily exercise, to mention a few. Harding and Van Wyck believed their regime consisting of a salt-poor, low caloric diet, restricted fluid intake, and bed rest explained their low toxemia rate. We have found this treatment of value in combating water retention and edema but consider its efficacy in preventing actual toxemia as not yet clearly proved.

Some authors, while ascribing great importance to large weight gains, have further stated that lesser gains also have some significance. Among our 100 toxemia patients there were, in addition to the 61 with excessive gains, another 20 with weight increases at one or more periods exceeding the averages by 50 per cent or more. A glance at Table II of our previous report shows that such gains were also frequent with normals. Furthermore, an examination of 100 unselected normal patients showed that, besides the 40 with excessive gains, there was among the remaining 60 a group of 28 who had gains of at least 50 per cent above the averages one or more times during the last four months. The proportion, then, for toxemia (20 out of 39) was only slightly greater than that for the normals (28 out of 60).

Several observers have stressed the *sudden* large weight gain as particularly indicative of impending toxemia. A study of our 61 toxemia patients with excessive gains showed that there were 17 in which the gains could be considered sudden and unexpected as they were preceded for one or more observation periods by average or less than average increases. A second group of 29 had excessive increases which were less abrupt, since the previous gains were more than average though less than 50 per cent plus. The remaining 15 had excessive gains following large increases of 50 per cent or more above the average and therefore were in no way sudden or unexpected. As a comparison, 100 normal patients (unselected except for parity to correspond with the toxemias) showed 40 with excessive gains, of which the numbers occurring in the above three groups in order were 8, 15, and 17. The percentage incidences for the toxemia and normal patients with excessive gain were: First group (with sudden gain), toxemia 27.9—normal 20.0; Second group (less sudden), toxemia 47.5—normal 37.5; Third

TABLE IV. A COMPARISON BETWEEN NORMAL AND TOXEMIA PATIENTS IN REGARD TO THE SUDDENNESS OF EXCESSIVE WEIGHT GAINS—AS EVIDENCED BY THE EXTENT OF PREVIOUS WEIGHT INCREASES

	PATIENTS WITH EXCESSIVE GAINS	
	NORMAL (40)	TOXEMIA (61)
Increase average or less than average before onset of excessive gain	20.0%	27.9%
Increase more than average but less than 50 per cent plus before excessive gain	37.5%	47.5%
Gains of 50 per cent or more above average before excessive gain	42.5%	24.6%

necrosis rarely causes noticeable symptoms. The public is only inadequately served by so-called "early diagnoses" campaigns urging individuals with certain symptoms to submit to an examination. The most such efforts can accomplish is to uncover a limited number of well-advanced cases. An amazing number of people with extensive and occasionally spectacular disease do not have enough symptoms to arouse the suspicions of the patient himself, his family, or even his physician. It is significant that more than 80 per cent of all cases of tuberculosis reported to health departments are already in an advanced stage.⁵

The logical conclusion is that in order to find tuberculosis at an early stage—to find it reliably at any stage—it is necessary to make the roentgenologic examination routine even for "healthy" persons.

In 1932 Bloch and his associates in the chest division of the University of Chicago Clinics began a series of roentgenologic group examinations on students and employees. In 1934 they widened the scope of this work to include the patients attending the prenatal clinic of the Chicago Lying-in Hospital. These patients were invited to report to the Chest Clinic for a fluoroscopic examination free of charge. Of the 6,298 patients attending the prenatal clinic from Feb. 14, 1934, to April 1, 1937, 4,040, or 64 per cent, reported for this examination (Table I). These patients were unselected except for the exclusion of known or suspected cases of tuberculosis. The entire group were of the white race. All patients showing definite or suspected lesions by fluoroscopy were referred for stereoscopic roentgenograms. Seventeen patients in whom tuberculosis was suspected on fluoroscopy did not report for roentgenograms. Forty-three, or 1.06 per cent, of fluoroscoped group were shown to have tuberculous changes of clinical importance. Of these 28, or 0.7 per cent, had active tuberculosis. We would like to emphasize that these cases of tuberculosis were unsuspected. It is not probable that they would have been diagnosed if routine fluoroscopic examinations had not been carried out.

We believe that in order to obtain fully satisfying results, these examinations will have to be made obligatory.* Four of the 17 patients who had fluoroscopic findings but no roentgenograms canceled their clinic registration when asked to have chest films. It seems to us that the percentage of active tuberculosis might have been higher if all the clinic patients had been fluoroscoped, for it is probable that some of these women refused roentgenograms because of the fear of tuberculosis, and some may even have been attempting to conceal past disease.

In addition to tuberculosis, several nontuberculous pulmonary and extrapulmonary conditions were found. Cardiac enlargement or pathologic cardiac contour was described in 205 cases and suspected in an additional 170 cases. In these, organic heart disease was diagnosed clinically in 181, or 4.5 per cent, of the fluoroscoped cases. We attribute this discrepancy to the fact that the cardiac displacement in late pregnancy may simulate cardiac enlargement on fluoroscopy. There were also three cases of bronchiectasis, and one case each of substernal thyroid, calcified thyroid, calcified pleura, tumor of the pleura, and spontaneous pneumothorax.

The reliability of chest fluoroscopy as a case finding method in tuberculosis has been questioned by some on the basis that it is too subjective

*At the present time we are fluoroscoping nearly 100 per cent of the prenatal patients by making this procedure a part of their general examination on their first clinic visit.

UNSUSPECTED TUBERCULOSIS IN PREGNANT WOMEN AS REVEALED BY ROUTINE ROENTGENOLOGIC EXAMINATIONS*

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WHEN pregnancy occurs in a woman who has tuberculosis, a serious problem confronts the physician. It is not our purpose to review the extensive literature on this subject. However, the opinion is generally held that pregnancy creates a grave additional hazard for the tuberculous woman, and it may aggravate the disease and even menace her life. Furthermore, the newborn baby of a mother with undiagnosed tuberculosis is very likely to contract the disease from its mother. Conservative estimates have placed the incidence of active tuberculosis in the "healthy" population at 1.5 per cent.¹ It is only reasonable, then, that our standards for efficient prenatal care should include an effective method for detecting the presence of tuberculosis. It is our purpose to present data which indicate that sufficient unsuspected tuberculosis can be found by routine chest fluoroscopy to justify its use in all prenatal patients.

There has been a growing conviction of the inadequacy of the physical examination as a means of detecting the presence of pulmonary tuberculosis and the importance of roentgenologic diagnosis has been ever increasing. Responsible physicians will no longer rule out the presence of pulmonary tuberculosis on the basis of a physical examination alone, for they realize that even the most skilled examination often fails to reveal the presence of significant pathology.

This fact has been demonstrated by various workers in the field of tuberculosis. Kayser-Petersen's recent extensive review² indicates that from 10 to 60 per cent of all cases of tuberculosis which were found on x-ray examination had been missed on physical examination. Five years ago, Bloch estimated, on the basis of the experience of the chest division of the University of Chicago Clinics, that about one-third of all cases of clinically important lung disease are missed on physical examination.³ Now he believes that one-third is too conservative an estimate.¹ Sampson and Brown⁴ in their careful study of 1,004 patients at Trudeau Sanatorium found no physical signs of disease in 39.6 per cent, and physical signs indicating less disease than the roentgenogram in an additional 36 per cent.

The absence or scarcity of symptoms is increasingly acknowledged as another cause of failure to make the diagnosis of tuberculosis in many cases. Tuberculosis which has not advanced into the stage of tissue

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Part of this paper was taken from a more comprehensive report of group roentgenologic examinations made at the University of Chicago Clinics. A complete report of the data obtained in this survey entitled "Roentgenological Group Examinations for Pulmonary Tuberculosis" by Bloch, Francis, Eisele and Mason, was presented at the Fifth International Congress of Radiology, in Chicago, September, 1937, and was published in "The American Review of Tuberculosis" 37: 174, 1938.

advanced tuberculosis can be diagnosed quite easily this way. It should be emphasized that the fluoroscopic examination is used only as a screen in case finding surveys, but never to rule out the possibility of lung disease where there are symptoms. Nor is it reliable for making a definitive diagnosis, or as a means of following the course of a tuberculous lesion. For these purposes, roentgenograms are essential.

Tuberculin tests as a screening method have been used instead of a roentgenological method chiefly in examining school children. Apparently they can be used successfully in children. It is not the purpose of this paper to compare the reliability of the tuberculin test and fluoroscopy as screening methods. However, we concluded that the fluoroscopic method would be more efficient in most adult groups. The first difficulty in applying the tuberculin test to adult groups is the necessity for a return visit at a specified time for the reading of the test. A lack of adequate patient cooperation on this point would probably lead to failure in many instances. An additional and more important objection is the fact that a large number of clinically nontuberculous adults react to tuberculin. In urban populations, a majority of adults are positive reactors. If a tuberculin survey is to be of practical value, it would be necessary that all positive reactors have a roentgenologic follow-up at considerable expense of money and time. At the same time a small percentage of clinically tuberculous people do not react, or react only very weakly, to tuberculin. We believe that present methods of tuberculin testing do not present us with as accurate a picture of the true status of adult clinical tuberculosis as the more direct roentgenologic method.

A study of the reported incidence of tuberculosis in comparable groups of obstetric patients (Table II) further substantiates the opinion that when physical examination and history taking alone are relied upon, even when carried out by careful clinicians, many cases of tuberculosis remain undiagnosed. Allen and Bauer⁷ reported the incidence of medical complications in 9,696 consecutive pregnancies from Presbyterian Hospital and Rush Medical College out-patient department (Chicago). They reported seven cases of tuberculosis, or an incidence of 0.07 per cent. Tarnis and Clahr⁸ report that in 1,909 obstetric patients, seen during 1934 in the prenatal clinic of the Morrisania City Hospital (New York), no cases of tuberculosis were found. All were charity patients. Royston, Jensen, and Hauptman⁹ report 51 cases of tuberculosis in 13,570 obstetric patients at the St. Louis Maternity Hospital and out-patient department, an incidence of 0.37 per cent. The authors point out that this is not a true incidence because some of the patients were referred from elsewhere because of the tuberculosis. It may be noted also that 19, or 37 per cent, of the tuberculous patients were negroes. At the Chicago Maternity Center¹⁰ 17,733 women were registered for confinement care in their own homes from July 1, 1932, to June 30, 1937. Approximately one-third of these patients were negroes. Ten patients were found to have tuberculosis (including two cases of tuberculous meningitis and one case of milary tuberculosis). In ad-

and therefore is open to error. However, it has been noted that the accuracy of the method increases directly with the increased experience of the examiner.¹ The superiority of chest roentgenograms over fluoroscopy cannot be questioned, but the expense of films has made it impractical for many group examinations. Most authors agree that excellent results can be obtained with fluoroscopy if roentgenograms are made on all persons with definite or suspicious findings fluoroscopically. We do not believe that many tuberculous lesions of clinical importance are overlooked by an experienced examiner who is trained in fluoroscopic technique and in lung pathology. However, it is true that in inexperienced hands considerable pathology may be missed. Certainly all

TABLE I. ROUTINE FLUOROSCOPIES ON UNSELECTED CASES (EXCEPT FOR THE EXCLUSION OF KNOWN TUBERCULOSIS), BETWEEN FEBRUARY 14, 1934, AND APRIL 1, 1937

		NUMBER	PER CENT
Total clinic patients		6,298	100.0
Fluoroscoped patients		4,040	64.0
Not fluoroscoped:			
No known tuberculosis		2,209	35.2
Known tuberculosis		49	0.8

I. TUBERCULOSIS	NO.	PER CENT OF FLUOROSCOPED CASES	II. CARDIAC PATHOLOGY	NO.	PER CENT OF FLUOROSCOPED CASES
1. Clinically important tuberculosis, proved by subsequent roentgenograms:			1. Fluoroscopic findings:		
a. Active	28	0.69	a. Hearts considered to be enlarged and/or of pathologic contour	205	5.1
b. Inactive	15	0.37	b. Hearts questionably enlarged and/or of pathologic contour	170	4.2
Total	43	1.06	Total	375	9.3
2. Suspicious findings but patients failed to get roentgenograms (4 patients canceled their clinic registration when asked to have chest films)	17		2. Final diagnosis in above cases:		
Summary:			a. Organic heart disease	158	3.9
Tuberculosis found on fluoroscopy	43		b. Probably organic heart disease	23	0.6
Known tuberculosis	49		Total	181	4.5
Total tuberculosis	92		c. No organic heart disease	119	
If incidence of 0.69% was maintained there were 15 additional cases of active tuberculosis undiscovered among the unfluoroscoped patients			(apparent enlargement due to cardiac displacement in late pregnancy)		
			d. Inadequate observation for definite diagnosis	75	

MISCELLANEOUS	NO.
1. Bronchiectasis	3
2. Substernal thyroid	1
3. Calcified thyroid	1
4. Calcified pleura	1
5. Tumor of the pleura	1
6. Spontaneous pneumothorax	1

undiagnosed syphilis discovered by routine Wassermann and Kahn tests. This gives an incidence of 0.87 per cent for the 6,298 patients attending the clinic during this period. This figure is comparable to the incidence of 1.06 per cent of the unsuspected tuberculosis in our fluoroscopic series. It is a reasonable conclusion, then, that routine roentgenologic examinations of the chest rank with routine Wassermann tests as a medical necessity in pregnant women. One may argue that the problems of syphilis and tuberculosis in pregnancy are not the same, that syphilis is of greater importance because of the danger of transmission of the disease to the fetus. However, though prenatal infection of the fetus with tuberculosis has never been conclusively proved, and if it does occur, it is so rare as to be of no clinical importance, there is grave danger of the newborn infant contracting the infection from its mother.

In recent years, the much publicized decline of the mortality rate from tuberculosis has led to the belief that the disease is getting well under control. Although tuberculosis has moved from first to seventh place as a cause of death in the general population, for the age groups involving obstetric patients tuberculosis still ranks first as a cause of death.

SUMMARY AND CONCLUSIONS

1. The inadequacy of symptoms and physical examination as means of discovering pulmonary tuberculosis has been discussed.

2. Routine chest fluoroscopy, followed by roentgenograms in all cases with definite or suspected lung pathology, is a satisfactory method of finding tuberculosis when carried out by an experienced examiner trained in fluoroscopic technique and lung pathology.

3. Application of this method to 4,040 pregnant women, unselected except for the exclusion of known tuberculosis, disclosed 43 cases of unsuspected tuberculosis or an incidence of 1.06 per cent. Twenty-eight cases, or 0.7 per cent, were shown to be active during the pregnancy.

4. The incidence of 1.06 per cent for unsuspected tuberculosis is approximately the same as the incidence of 0.87 per cent for unsuspected syphilis discovered by routine Wassermann and Kahn tests carried out in the same clinic over the same period of time.

5. Routine chest roentgenologic examinations should rank with routine Wassermann tests as a medical necessity in pregnant women.

6. Tuberculosis in pregnant women is still an important problem, for tuberculosis remains as the leading cause of death in this age group.

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dition, there were 8 cases of suspected tuberculosis which could not be followed adequately for final diagnosis. It is of interest that of the 21 maternal deaths occurring in this series, 5, or 24 per cent, were due to

TABLE II. THE INCIDENCE OF TUBERCULOSIS REPORTED IN OBSTETRIC GROUPS IN WHICH ROUTINE ROENTGENOLOGIC EXAMINATIONS WERE NOT MADE

AUTHORS	INSTITUTION	PATIENTS IN SERIES	CASES OF TUBER- CULOSIS	IN- CIDENCE PER CENT	COMMENT
Allen and Bauer	Rush Medical Col- lege O.P.D. and Presbyterian Hospital, Chica- go	9,696	7	0.07	
Tamis and Clahr	Morrisania City Hospital, New York	1,009	0	0.0	All charity pa- tients; negroes included
Royston, Jen- sen, and Hauptman	St. Louis Mater- nity Hospital and O.P.D.	13,570	51	0.37	Some referred from elsewhere because of tu- berculosis; 37 per cent of pa- tients with tu- berculosis were negroes
Tucker	Chicago Maternity Center	17,739	18	0.10	Ten cases proved; 8 cases suspect- ed. All patients registered for home delivery. About one-third of group were negroes
Total		42,014	76	0.18	

tuberculosis. It would seem that in all of these groups the economic and social status was equal to, or lower than, that of our group. Many negroes were included whereas our group was from the white race exclusively. In the combined groups, totaling 42,014 patients, there were 76 cases of tuberculosis (including suspected cases). If routine roentgenologic examinations had been made, one could reasonably expect six times as many cases.

Today one does not question the advisability of the use of routine Wassermann and Kahn tests to discover syphilis in pregnant women. The number of cases of unsuspected syphilis so discovered has more than justified making this a routine procedure. However, an equal justification for routine chest fluoroscopies has not hitherto been recognized. Therefore, we have compared the incidence of unsuspected syphilis with the incidence of unsuspected tuberculosis discovered by the respective routine examinations in our clinic. During the same period that our fluoroscopic survey was made, there were 139 patients with some degree of positiveness in either the Wassermann or Kahn, or both. After further serologic and clinical investigation, 45 of these were considered to be nonsyphilitic. Of the 94 remaining cases, 39 had previously received antisyphilitic treatment. Thus, there were 55 cases of unsuspected and

When our investigation was begun in 1934 there had been no studies recorded on this particular phase of the sedimentation test except those in an article published by Grodinsky.²

TABLE I. ACUTE PELVIC INFLAMMATORY DISEASE

Total number of patients	30	
Normal sedimentation rate	3	10 per cent
Abnormal sedimentation rate	27	90 per cent

TABLE II. ACUTE PELVIC INFLAMMATORY DISEASE SEDIMENTATION RATE IN ONE HOUR

RATE	PATIENTS	PER CENT
3-10 mm.	3	10.0
11-20 mm.	12	40.0
21-30 mm.	13	43.3
31-40 mm.	2	6.6

He reported quite a large number of patients with various conditions, among them being groups with appendicitis and pelvic inflammatory disease. Patients with both chronic and subacute appendicitis as well as with the acute type were noted in the appendiceal group. It was not specified whether the patients with pelvic inflammatory disease noted in his series suffered with an acute condition or exhibited chronic lesions.

In 1935 Lesser and Goldberger³ reported a large series of patients among whom were a considerable number with acute appendicitis and pelvic inflammatory disease. They studied 1,000 cases of the latter, but they did not mention the time elapsing between onset of the pain and the time when the blood was taken for examination. It was not apparent whether the diagnoses in the appendiceal group were simply based on clinical grounds or were verified by the pathologist. Their conclusions regarding the differential value of the test were as follows:

1. The sedimentation reading in cases of acute appendicitis is uniformly normal.
2. The sedimentation readings of all other acute abdominal conditions are consistently abnormal.

It has been stated by Nicholson, and Gruenfeld and others⁵ that the sedimentation rate in acute catharrhal appendicitis is always normal. This may be true if such a condition is demonstrable. Dr. Baxter L. Crawford,⁶ Director of the Pathologic Laboratories at Jefferson Hospital has stated that acute catarrhal appendicitis is rarely seen in the pathology laboratory. Usually the condition has progressed to a more advanced state before operation has been performed. Therefore it is essential that the test, to have positive value, must be applicable to those cases of appendicitis which have not ruptured or become abscessed.

Bannick, Gregg and Guernsey⁴ in a recent article on various phases of the sedimentation rate also studied a series of patients with pelvic inflammatory disease and acute appendicitis. Their conclusions are similar in some respects to those of Lesser and Goldberger. They state that over a two-year period they have not encountered a single case in which the sedimentation rate was definitely increased as a result of appendicitis, unless rupture had occurred.

The only paper published which takes into consideration the duration of pain prior to the blood being taken for examination is one by Smith, Harper and Watson⁷ who employed the Linzenmeier technique in their studies. They concluded that the rapidity of blood sedimentation was of differential value between acute appendicitis and acute pelvic inflammatory disease, if a comparatively short time had elapsed between the onset of the pain and performance of the test.

A brief description of the plan used in our investigation is indicated in order to show more clearly the precise nature of the study and its possible value.

AN EVALUATION OF THE SEDIMENTATION TEST IN THE DIFFERENTIAL DIAGNOSIS OF ACUTE PELVIC INFLAMMATORY DISEASE AND ACUTE APPENDICITIS*

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THE study presented was undertaken for the purpose of evaluating the sedimentation test as a diagnostic aid in differentiating between acute pelvic inflammatory disease and acute appendicitis.

The conclusions are based upon a study of thirty patients with pelvic inflammatory disease and one hundred patients with acute appendicitis, admitted to the Receiving, Gynecological, and General Surgical Wards of the Jefferson Medical College Hospital from September, 1934 until November, 1937.

The value of the sedimentation test has been definitely established by numerous observers, and this is especially true in gynecology. The theories as to why the blood cells settle more rapidly in certain pathologic conditions, and less rapidly in others have been thoroughly discussed by various investigators, but there is apparent disagreement as to the actual cause. Nicholson¹ states in "Laboratory Medicine" that there is no adequate explanation of the phenomenon. A discussion of this phase of the subject is without the scope of this presentation; consequently this aspect of the problem will not be discussed.

We have observed over a long period of years that patients suffering with well-developed pelvic inflammatory disease always have a rapid sedimentation rate. This test, while possibly superfluous in making a diagnosis of advanced pelvic inflammatory disease, is valuable for other well-known reasons. Hence it occurred to us that if the test were performed at the onset of suspected acute appendicitis or acute pelvic inflammatory disease, before the diagnosis had been definitely established, it might prove to be of decided value. It is probable in most instances that the physician is called to see the patient with lower abdominal pain within the first twenty-four or forty-eight hours. This is the strategic time, when diagnostic acumen is often taxed to the utmost, for the patient may have a surgical abdomen, which if not cared for promptly may result in disaster. On the other hand, surgical interference may have harmful consequences, especially in the young woman of childbearing age. The (two) conditions which most frequently confuse the general surgeon and the gynecologist in establishing a differential diagnosis are acute appendicitis and pelvic inflammatory disease, in the early stage when the pain is still localized in the right lower quadrant.

*Read at a meeting of the Obstetrical Society of Philadelphia, January 6, 1938.

pelvic inflammatory disease. The plan therefore secured for study two groups of patients paralleling each other as closely in history, examination, and subsequent course as possible.

Due to the numerous methods and modifications of the sedimentation test, it is a bit difficult to convert the results of one method into those of another. The three most frequently employed methods are those of Cutler, Linzenmeier, and Westergren or a modification of one of these techniques. Regardless of the method used, the underlying principle of the sedimentation test is based on the fact that the red blood cells settle more rapidly in certain pathologic conditions than in normal individuals. Greisheimer, Treloar and Ryan⁸ made a study of the interrelation of the three methods mentioned and concluded that the average sedimentation in one hour in the case of normal individuals appears to be reasonably consistent.

Cutler's⁹ method of estimating blood sedimentation has been used in this study, since we have followed this technique routinely on the Gynecological Service for approximately ten years. The results are recorded on a chart which instantly shows the rapidity with which the blood cells settle. The procedure is as follows: Aspirate 0.5 c.c. of 3 per cent sterile sodium citrate solution into a 5 or 10 c.c. syringe. Into the same syringe draw venous blood up to the 5 c.c. mark; mix gently and force the contents into a small glass (Cutler) tube, graduated to 50 mm. Take readings every five minutes for one hour, after closing tube with a paraffin covered cork, inverting it carefully and placing it upright in a rack, certain that it is vertical and that the level of the citrated blood is exactly at the zero graduation mark. The readings are charted graphically.

Our interpretation of the test is that in healthy women the blood will sediment from within 2 to 10 mm. in one hour. When blood settles faster than 10 mm. in one hour we consider it abnormal.

Table I shows that in a series of 30 patients with acute pelvic inflammatory disease 90 per cent sedimented more rapidly than normal.

Table II shows in detail that the highest percentage of patients with acute pelvic inflammatory disease have a sedimentation rate between 11 and 40 mm. in one hour.

Table III indicates the hours elapsing between the onset of symptoms and the time that the blood was taken for the test. It will be noted that the greater percentage were taken between five and fifty hours. Only one patient had pain for 100 hours before the test was performed.

TABLE III. ACUTE PELVIC INFLAMMATORY DISEASE

LAPSE OF TIME BETWEEN ONSET OF PAIN AND RECORDING OF SEDIMENTATION RATE

HOURS	PATIENTS	PER CENT
5-25	15	50.0
26-50	11	36.6
51-75	1	3.3
76-100	3	10.0

TABLE IV. ACUTE PELVIC INFLAMMATORY DISEASE

LEUCOCYTE COUNT	PATIENTS	PER CENT
5,000-10,000	1	3.3
10,000-15,000	10	33.3
15,000-20,000	11	36.6
20,000-30,000	8	26.6

The patients accepted for inclusion in the pelvic inflammatory group were subject to a definite diagnosis of acute pelvic inflammatory disease, based upon the following criteria:

I. History:

- a. Onset, location and duration of pain in hours, prior to performance of test.
- b. Elimination of previous attacks.
- c. Relation of onset of pain to menses.
- d. Vaginal discharge.
- e. Urinary symptoms.
- f. Exclusion of demonstrable pathology elsewhere.

II. Examination:

- a. Inspection of vulva, urethra, Skene's ducts, Bartholin's glands, and cervix with microscopic examination of discharge if present.
- b. Bimanual examination, excluding those patients with adnexal enlargements.
- c. Temperature, pulse, respiration.
- d. White blood cell count.

It might be interesting at this point to explain why we have a relatively small number of patients in the acute pelvic inflammatory group. We found that the greater proportion of patients with pelvic inflammatory disease observed in the receiving and gynecologic wards, and in the out-patient department either presented recurrent attacks, illness of longer duration than from twenty-four to seventy-two hours or definite pelvic masses. We did not accept patients with this type of pathology, since we desired to study a group closely resembling acute appendicitis in history and examination.

In selecting patients for the appendiceal group, the following criteria were required as a basis for study:

I. History:

- a. Onset, location and duration of pain in hours prior to performance of the test.
- b. Elimination of patients with histories suggestive of chronic or sub-acute appendicitis.

II. Examination: -

- a. Abdominal and pelvic examination.
- b. Temperature, pulse and respiration.
- c. White blood cell count.

III. Operative Findings:

- a. Patients with acute appendicitis, either catarrhal, suppurative, or gangrenous, only were accepted.
- b. Elimination of patients with ruptured appendix or appendiceal abscess.
- d. Histologic examination of all removed appendices.

Patients with chronic and subacute appendicitis were not accepted because we wished to include only those with acute appendicitis verified by pathologic examination. Likewise, patients with ruptured and abscessed appendices were rejected because the longer duration of their conditions not infrequently resembles the physical signs of advanced

In Table IX a comparative picture of both acute appendicitis and acute pelvic inflammatory disease in relation to the rapidity of the blood sedimentation is shown on a percentage basis.

SUMMARY AND CONCLUSIONS

1. Groups of patients with acute appendicitis and acute pelvic inflammatory disease comparable as to duration of symptoms and extent of pathology have been studied with the sedimentation test in an attempt to determine whether or not it is of value in differentiating the two conditions.

2. Ten per cent of the patients with acute pelvic inflammatory disease had a normal sedimentation rate, while 90 per cent were abnormal.

3. Forty-eight per cent of the patients with acute appendicitis had a normal sedimentation rate, while 52 per cent were abnormal.

4. We cannot agree with the reports of some observers that the sedimentation rate is never abnormal in acute appendicitis unless rupture or abscess formation has occurred; on the other hand our findings are quite in accord with those of others in regard to the sedimentation rate in acute pelvic inflammatory disease.

5. Our conclusions are that the test per se cannot alone be relied upon to differentiate between the two conditions, since in practically half of the patients suffering with acute appendicitis, sedimentation was abnormal.

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DISCUSSION

DR. J. W. CUTLER.—For a number of years there have appeared an increasing number of papers emphasizing the necessity of correcting for anemia to make possible a more accurate evaluation of the sedimentation test. Those who hold this view believe that anemia when present materially increases the sedimentation rate so that the latter not only reflects the activity of the disease, but also the associated anemia. They also believe that one can isolate the anemia factor and correct for it by the simple procedure of subtracting sufficient plasma to bring the cell count to 5,000,000 before performing the test. The difference between the sedimentation rate of the corrected sample and the uncorrected or anemia sample would, in their opinion, represent the increased sedimentation brought about by the anemia factor itself.

In the past two and one-half years Park, Herr, and I have studied this question quite thoroughly and have come to the conclusion that anemia has little to do with the phenomenon of blood sedimentation and that one cannot correct for anemia and obtain consistent sedimentation findings. Our difficulty lies in our methods for recording sedimentation rates.

There is clinical evidence to show that marked anemia can be associated with a slow sedimentation—for instance, bleeding peptic ulcer, sickle cell and pernicious anemia. Experimentally, we can make cells, regardless of the number in suspension, sediment rapidly or slowly by adding certain substances to the plasma. If anemia

Table IV shows that in 52 per cent of the patients with acute appendicitis, the sedimentation rate was abnormal.

Table VI exhibits in detail the varying degrees of rapidity with which sedimentation took place in 52 per cent of the patients with acute appendicitis, not actually as rapid as in the acute pelvic inflammatory group (Table II) but relatively so.

Table VII shows the lapse of time between the onset of symptoms and the recording of the sedimentation rate in the patients with acute appendicitis. The similarity to Table III in the acute pelvic inflammatory group is readily noted.

Table VIII shows the grouping of leucocyte counts in the patients with acute appendicitis. Ninety-one per cent were relatively high.

TABLE V. ACUTE APPENDICITIS

Total number of patients	100	
Normal sedimentation rate	48	48 per cent
Abnormal sedimentation rate	52	52 per cent

TABLE VI. ACUTE APPENDICITIS. SEDIMENTATION RATE IN ONE HOUR

RATE	PATIENTS	PER CENT
1-10 mm.	48	48
11-15 mm.	26	26
16-20 mm.	16	16
21-25 mm.	10	10

TABLE VII. ACUTE APPENDICITIS. LAPSE OF TIME BETWEEN ONSET OF PAIN AND RECORDING OF SEDIMENTATION RATE

HOURS	PATIENTS	PER CENT
5-25	59	59
26-50	26	26
51-75	9	9
76-100	6	6

TABLE VIII. ACUTE APPENDICITIS

LEUCOCYTE COUNT	PATIENTS	PER CENT
5,000-10,000	9	9
10,000-15,000	43	43
15,000-20,000	36	36
20,000-30,000	12	12

TABLE IX. COMPARISON OF THE SEDIMENTATION RATES

SEDIMENTATION RATE	ACUTE APPENDICITIS	ACUTE PELVIC INFLAMMATORY DISEASE
Normal	48 per cent	10 per cent
Abnormal	52 per cent	90 per cent

Comparison with Table IV is especially interesting when we note that 43 per cent of the patients with acute appendicitis had a leucocyte count between 10 and 15 thousand, while 33.3 per cent of the acute inflammatory cases fell within the same limits. Thirty-six per cent of the patients with acute appendicitis had a leucocyte count between 15 and 20 thousand while 36.6 per cent of the pelvic inflammatory cases also had a leucocytosis between 15 and 20,000. This would suggest that it might be unwise to allow the leucocyte count alone to influence one in establishing a differential diagnosis.

THE MANAGEMENT OF BREECH DELIVERIES*

BASED ON A REPORT OF 709 CASES FROM THE PHILADELPHIA
LYING-IN HOSPITAL

ROY W. MOHLER, M.D., PHILADELPHIA, PA.

INTRODUCTION

BREECH presentations and their management in labor are problems which are interesting to all who do obstetrics. It is a well-known fact that the danger to the child who presents by the breech is much greater than to the one which presents by the vertex. Because of an appreciation of this danger in 1931 we reviewed 170 cases of breech presentations and reported them to this Society. The gross fetal and neonatal mortality was 7.9 per cent, which is about three times higher than the corrected fetal mortality for the whole group of patients delivered at the Philadelphia Lying-in Pennsylvania Hospital. Because of the original report, and the conclusions drawn from it, certain policies in the management of breech presentations were adopted. These recommendations were that all breech cases should be completely studied clinically and with x-ray, and the size of the child in relation to the size of the maternal pelvis should be considered carefully in the management of breech presentations, and that some member of the attending Staff should be present at all breech deliveries. Since the time of the original report, these recommendations have been carried out in complete detail. All breech presentations recognized during the prenatal period examinations, have had complete x-ray studies done, and measurements made according to the Ball technique. If the x-ray studies showed an unusually large baby or evidence of fetopelvic disproportion, a consultation between various members of the Staff was called, and a decision as to the type of delivery to be chosen was made.

An absolute rule for management of breeches which we think has been quite worth-while, is to have a member of the attending Staff present and ready to deliver every breech admitted to the hospital. The House Officer is given the opportunity to get experience in the management of the case, and is allowed to proceed only so long as no obstacle appears, in which case the attendant in charge proceeds with the delivery.

During the period of time extending from Jan. 1, 1930, to Oct. 1, 1937, 709 breech presentations were delivered at the Philadelphia Lying-in Pennsylvania Hospital. It was found that breech presentations occurred very frequently in premature labor, and this incidence can be explained by certain hypotheses which may be tenable. One

*Read before the Obstetrical Society of Philadelphia, December 2, 1937. In a Symposium on Breech Deliveries.

is added the cells settle rapidly, if lecithin is added, they sediment extremely slowly. The reason why some cells sediment rapidly and others slowly is not because of any difference in the size or shape or number of the cells, but whether or not they form large aggregates. If they do, they sediment rapidly, and vice versa. The ability to form large aggregates is a function of the plasma and depends on the presence in the plasma of certain substances such as globulin and fibrinogen. These substances not only have a quantitative relationship to the sedimentation rate, but also a qualitative one. Globulin, for instance, will cause more rapid sedimentation than fibrinogen. When plasma is removed, in an endeavor to correct for anemia, then the very factors responsible for sedimentation are also removed. If a large quantity of plasma is removed as is necessary when the anemia is marked, the mechanism of rouleaux formation is seriously interfered with and sedimentation may become so slow that the laboratory may report a normal sedimentation finding in the presence of clinically active disease. Those who believe in correction explain this observation as overcorrection, although the blood count of the corrected sample is 5,000,000, as in other corrected samples. This observation is not overcorrection. It is a deliberate interference with the mechanism of aggregation of red cells to the point that the sedimentation phenomenon disappears.

As a corollary of the above study, I am further convinced that our present methods for recording sedimentation rate need considerable modification. What is needed is a more scientific unit for expressing blood sedimentation, one that will express sedimentation in terms of velocity or the rate at which the aggregates settle in a given unit of time.

When such a unit will be developed, it will be independent of the size of the tube used, whether long or short, narrow or wide, since the rate of settling of the aggregates must be exactly the same in all tubes. Should such an effort be successful, then, I believe, blood sedimentation studies will take on greater clinical significance.

DR. BROOKE M. ANSPACH.—The sedimentation test gives us the most reliable signs of the degree of subsidence in pelvic inflammatory trouble. It is also a safeguard in any case, for it sometimes brings to our attention lesions other than pelvic which might exert an unfavorable influence in operative treatment. We have learned to expect a rapid rate in a secondary anemia. It has been rapid sometimes when a myoma was undergoing degeneration, and is usually so in carcinoma with ulceration and infection.

Leucocytosis is an almost immediate reaction to an acute inflammatory process, but an increase in the sedimentation rate does not begin for twenty-four to thirty-six hours. We need not be surprised with a rapid reaction in post-partal or post-abortal infections, since the sedimentation rate may have been rapid beforehand, as it is always increased in pregnancy. In the case of gonorrheal salpingitis the infection has been present in the woman for awhile before it reaches the tubes. Under these circumstances it is quite likely that the sedimentation rate has been rapid before the acute symptoms began. While we may be able in a large majority of cases to distinguish between acute appendicitis and acute gonorrheal salpingitis upon other grounds, I believe that this difference in the sedimentation rate will prove a very useful help in differential diagnosis.

As long as labor continues it is allowed to progress until the breech or presenting part has delivered through the vaginal outlet. When necessary, just before the presenting part has delivered, gas-oxygen anesthesia is produced during the pains, and an episiotomy is done. As soon as the baby has been delivered to a point just at the umbilicus, a breech extraction is performed. Sometimes this extraction consists only in directing the body through its exit, but usually it consists in carrying out a definite technique and procedure.

TECHNIQUE OF PROCEDURE OF EXTRACTION BY VAGINA

When the breech has been delivered to the umbilicus, complete gas-oxygen anesthesia is induced. It is very important to wait for the extraction until the anesthesia is complete so that the movements of the patient do not interfere with the technique of the method chosen. With both hands the hips of the baby are grasped by the attendant, and the body of the child is rotated squarely under the arch of the symphysis. With gentle and firm traction, the body of the child is delivered until the tips of the scapulae are visible under the symphysis. During this manipulation a trained assistant locates the head of the baby through the abdominal wall and follows its descent toward the pelvis; an effort is made to keep the head flexed and the descent must be slow, being always mindful of the fact that the arms may become extended. When the scapulae show from under the symphysis pubis, the shoulders have a tendency to rotate into an anteroposterior position, and with continued gentle traction at about 135 degrees, the anterior arm will deliver either spontaneously, or with slight traction in the posterior axillar fold. After the delivery of the anterior arm, the body of the child is rotated 180 degrees through an arc in the opposite direction. This maneuver will convert the undelivered arm into an anterior arm, and it can be delivered as the first one.

After the arms have been delivered, the head is directed into the pelvis, and is manipulated into a direct anteroposterior position by firm and properly directed pressure from above, and gentle traction from below. At this point the aftercoming head forceps, as devised by Dr. Edmund Piper, are applied, with the body of the child held in an extended position above the symphysis of the mother. Great care must be exercised in this maneuver so that there is no injury to the child's body. After application of the aftercoming head forceps, the head is delivered by making traction with the forceps and combining the traction with a slight effort at flexion. No effort must be made to hurry any of these maneuvers and no strenuous force should be applied. The force used must be well distributed and directed so that it will do no injury to the child.

In those deliveries where labor does not progress normally, a decomposition and extraction of the child is done under deep surgical anesthesia, providing the cervix is completely dilated and effaced. No effort is made to deliver a baby through an undilated cervix. If de-

hypothesis which seems most plausible is based on the assumption that definite polarity of the child does not occur until the presenting part has become fixed in the inlet of the pelvis. It seems to me that the deaths of premature and immature infants that occur following premature breech deliveries should not be attributed to the form of delivery but to the fact that the labor was premature. If this exclusion is accepted, and if we also accept the exclusion of deformed and macerated babies, we still may anticipate a higher fetal mortality for infants delivered by breech than those delivering by vertex.

In any report on breech presentations, we must consider the fetal mortality brought about by the accidents caused by presentation and delivery as the important factor. The diagnosis of position is important, and it usually can be made without much difficulty in the patient near term. In patients with breech presentations who deliver prematurely, the diagnosis will usually be missed until labor is well advanced. For this reason, I shall confine my remarks to the management of patients with breech babies of normal vitality near term.

INCIDENCE

The incidence of breech presentation for the group of cases reported is usually 3.5 per cent. Stander in his text reports that the incidence in Schroeder's statistics was 3.11 per cent. In 50,000 deliveries at the New York Lying-in Hospital, the incidence was 3.9 per cent, and in 7,500 deliveries at the Johns Hopkins Hospital it was 3.9 per cent. The incidence at the Philadelphia Lying-in Pennsylvania Hospital, is 4.7 per cent for approximately 18,000 cases.

NOMENCLATURE

There is some confusion in the terminology applied to breech presentations. And since the type of breech one is dealing with is a factor in its management, I think I should give my understanding of the terminology used. A frank breech implies that the leg is flexed at the thigh and extended at the knee. A full breech implies that the leg is flexed at the thighs and the knees, and the term incomplete breech means that either one or both feet or knees are presenting.

In any consideration of breech deliveries, one must consider two methods of managing the patient. The first is to have the patient deliver vaginally if possible without too much danger to the child or mother. In those cases where vaginal delivery was the method chosen, the management was according to certain rules. As soon as labor was definitely established, analgesia was produced with nembutal and scopolamine, unless there was some contraindication to its use. The dose varied from 6 to 9 gr. of nembutal, and 1/100 or 1/150 gr. of scopolamine; the dose of nembutal varied somewhat according to the weight of the patient, and also because of the size of the routine dose which was being used over certain periods of time. At present, we are using 4½ to 6 gr. of nembutal with the original dose, and supplementing this dose later if necessary.

with a 7.9 per cent fetal mortality for breech deliveries which occurred in a series of 170 patients which were previously reported, and also compares favorably with other large series of breech deliveries, the corrected fetal mortality for which is usually near 6 per cent.

CONCLUSIONS

I have presented an outline of the points which we at the Philadelphia Lying-in Pennsylvania Hospital believe are important in the management of breech presentations.

This paper is based on 709 consecutive breech deliveries which occurred after certain policies based on an analysis of 170 breech deliveries was formulated.

The important points we feel are as follows:

1. That x-ray study should be used late in the prenatal period to determine the relative size of the fetus and mother.
2. That it is safer for the baby to deliver a larger than average sized child presenting by the breech by cesarean section.
3. That all breech babies delivered by vagina should be extracted under light anesthesia after the breech has been delivered, and this extraction should never be undertaken by anyone who has not been adequately trained with supervised experience in the management of breech deliveries.
4. That all decomposition of breech babies should be accomplished under deep surgical anesthesia after the cervix is completely dilated.
5. That aftercoming head forceps should always be used after the head has become engaged.

1806 SPRUCE STREET

DISCUSSION

DR. EDWARD A. SCHUMANN.—I am firmly convinced that in the greater number of cases the cause of breech presentation is purely accidental, that the fetus of sufficient size to be held in the pelvis is caught with the breech down by a series of intermittent uterine contractions. This is based upon a study of a series of multiparas. In a minority only breech presentation occurs because the shape of the fetus or uterus demands such presentation for the better accommodation of the fetal body in the uterine cavity.

If we were able to distinguish between the types, the whole question of external version could be more easily solved. If the position is an essential one in which the fetus fits the uterus, external version is contraindicated. Most external versions I practice are back as a vertex the next time I see the patient. Furthermore, however little pressure may be required in turning the child, there is danger of producing an abnormal cephalic presentation. The matter of cord disturbance also still impresses me seriously. I do not believe that external version is a practice I would regularly follow.

With regard to the management, I wonder why it is necessary to extract the child when the umbilicus is delivered. If the umbilicus appears, the child will continue to come down. In spite of the essayists' account of the ease with which the arm delivers itself spontaneously with slight pressure, the arm sometimes offers a great deal of difficulty. Of course, if one follows the fundus from above, the danger of extension of the arm is minimized. The main thing is to maintain flexion and the more you maintain this the simpler the breech extraction. I would prefer to push rather than pull on the breech. If I were to extract a breech, I would prefer to do the decomposition early, when the breech appears at the vulva rather than

livery of the child is absolutely necessary before the cervix is completely dilated, an effort is made to dilate it manually, or if this is not possible or judicious, a cesarean section is performed.

In breech presentations where labor is long and progress slow with the membranes already ruptured for some time, a very serious problem confronts the attendant and each of these cases is a difficult situation which must be considered individually as it arises. It is this type of case which will always increase the fetal mortality for breech presentation unless we are able to anticipate them either before labor has begun or early in labor. Each of these difficult cases will be managed according to the individual's experience and judgment and according to the circumstances. No outline of the procedure necessary in such conditions will be touched upon except to remark that it is this type of case above all where it is certainly wise to resort to cesarean section before labor, or soon after labor has begun.

In cases when after a careful study it was learned that there was evidence of fetopelvic disproportion, or if the baby seemed larger than normal and the mother was not one with whom an undue risk should be taken, an elective cesarean section was performed.

In this group of 709 cases there were 58 cesarean sections. These patients had the sections performed after consultation with various members of the Staff and many of them had a trial of labor. Of this group of 58 cesarean sections, 40 were done because of a fetopelvic disproportion with a breech presentation, and the other 18 were done because of some accident of pregnancy in addition to a breech presentation. In this group there were 50 live babies and of the 8 babies lost, one of these was delivered from a patient where a large breech was the sole indication for the type of delivery chosen. The other 7 babies were lost because of other accidents of pregnancy, such as placenta previa, premature separation of the placenta, etc. In view of these statistics, we feel that our final decision to do a cesarean section on each of these cases was justified.

ANALYSIS OF STATISTICS

There were 709 breech presentations delivered at the Philadelphia Lying-in Pennsylvania Hospital during the period extending from Jan. 1, 1930, to Oct. 1, 1937. Of this group there were 295 primiparas and 414 multiparas. The gross fetal mortality was 186 babies, or about 26 per cent. In this group there were 49 babies from the 295 primiparas, and 98 babies from the multiparas, or a total of 147 babies that were lost because they were premature and nonviable, or deformed so that the type of presentation was not responsible for their deaths. There were 39 babies in the whole group which were lost and came under the list of corrected mortality, 18 from primiparas, and 21 from multiparas. These 39 babies represent a 5.5 per cent corrected fetal mortality for the whole group of babies presenting by the breech. This 5.5 per cent fetal mortality for breeches compares with a 2.5 per cent corrected fetal mortality for all patients delivered at the Philadelphia Lying-in Pennsylvania Hospital. The 5.5 per cent fetal mortality also compares

delivery in which interference is necessary, but the indication in my experience has been very rare. What I have always objected to was the teaching prevalent some years ago that just as soon as the cervix in a breech labor was dilated delivery should be effected. If this teaching is followed there is every reason in the world to lose babies.

Cesarean section has a definite indication in certain cases of breech, particularly with moderate pelvic contractions, or in old primiparas in whom the probability of another child may be remote. I use external version where possible in order to determine any disproportion between the head and the pelvis. This is my only indication for external version.

I feel that we are going back to the well-established methods which years ago governed the delivery of these cases. There is one recent advance, however, namely, the use of forceps on the aftercoming head, instead of old manual procedures. In every breech delivery the forceps should be prepared ready to put on if there is any retardation in the delivery of the head.

DR. COLLIN FOULKROD.—Too much stress has I feel been laid upon the normality of breech births. It is often the younger man who will allow the labor to go to the point of danger to the child, a condition more likely to occur in breech than in vertex presentations. In breech presentations the slowing up of the process of labor must therefore be watched more carefully than in a normal vertex, and interference practiced earlier if the conditions present should warrant it.

A relaxed multiparous uterus will be flaccid up until about one month prior to labor. Then during the period of settling with increased uterine contractions a breech may change to a vertex presentation. It is better therefore to wait until after the thirty-eighth week of gestation to try external version. With the usual multipara where the measurements are normal and the knowledge you have justifies you in trying external version, it is far better to wait until near term, to do the version, and then to rupture the membranes at the same sitting, by that means keeping the head in the pelvis and starting labor.

A breech will often go longer than the computed time of maturity, perhaps because the breech does not sink into the pelvic cavity as well. For reasons of disproportion a section may therefore be necessary.

DR. GEORGE ULRICH.—It is interesting to consider the cause of infant mortality in breech presentation. If you look up statistics you will find the lowest mortality is in the babies weighing from 7 to 9 pounds. Babies born in breech presentation and weighing less than four pounds are almost all lost; between four and five pounds, two-fifths are lost; between five and six pounds, less, and between seven and nine pounds, possibly not more than one-twentieth are lost. It is not the difficulty of breech delivery that causes the infant mortality, but the pressure on the premature head.

Waiting is a good policy, but how long should we wait? There is no indication for interference so long as the mother remains in good condition, the heart sounds of the baby hold to normal, and labor progresses. The criteria for interference should be the cessation of progress. The baby will very soon show the results of this.

Years ago we were taught two ways of delivering breeches; one by expression, and the other by extraction. Many women who have almost enough uterine force to push the breech over the perineum can be delivered by making slight pressure over the fundus of the uterus. This starts the breech over the perineum, stimulates contraction of the uterus and pushes the baby out.

One thing about aftercoming head forceps that every man must remember is never to use them until the head is engaged. I have seen infants killed and mothers maimed, just because this one little thing is forgotten. Also remember that the head cannot engage until it is first flexed. Flexion may be maintained by making pressure over the fundus of the uterus during traction.

DR. ALICE TALLANT.—The point about pressure on the fundus I once saw perfectly illustrated in the Charité Hospital in Berlin. The nurse on the Ward

to wait until the umbilicus comes down. Because I believe that the danger to the baby in breech is not asphyxia but intracranial traumatism, I am convinced that the longer the pelvic tissues are permitted to dilate and the oftener the baby is permitted to deliver spontaneously, the less will be the fetal mortality.

Dr. Wall, of Kensington, is presenting our own set of statistics. In that institution we practice the policy of noninterference whenever possible. Obviously, there are instances when progress is assisted, but we attempt to deliver the breech spontaneously whenever possible. As to the aftercoming head forceps, we use the instrument in all cases except where the head falls out before the forceps can be applied.

DR. NORRIS VAUX.—I do not believe in external version. I cannot see the reason for converting a breech to a vertex when nature has presented some abnormality or unusual condition in the lower uterine wall or pelvis which has caused the breech to become dependent. Furthermore if external version is done, I cannot agree with Dr. Mohler's comment on the subject, that the patient should be allowed to be ambulatory during the twenty-four hours following the procedure, because the placenta may be somewhat detached, the cord may become twisted around the child, or inadvertent rupture of the membranes may occur.

Breech presentation and delivery has its own mechanism similar to the mechanism of the vertex. If we understand this mechanism, and if the mechanism of breech is progressing normally, it is our practice to leave it alone, using analgesia, sedation and anesthesia where necessary, until the navel of the child appears. We do not assist it from there on unless the mechanism ceases to progress, and fortunately this does not often happen. The delivery is more likely to become obstructed when the shoulder girdle gets into the pelvic cavity. The remaining portion of the breech extraction or delivery, the aftercoming head, usually produces our greatest difficulty. The head must be kept flexed. The worst thing we can do is to pull on the breech that is descending, except to guide it.

We have no difficulty with what is called the decomposition, when the breech is arrested in midpelvis and the cervix is fully dilated. Extraction of an impacted breech, however, is a different consideration and is only attempted and performed under deep surgical anesthesia. Early episiotomy and aftercoming head forceps are used.

DR. ROLAND PORTER.—A small point I wish to bring out is that a fair proportion of breech cases change to vertex, especially in the multiparas with the globular uterus. That has been proved numerous times by comparing the x-ray in the dispensary and the later position when labor begins.

It is often said that after the baby is down to the umbilicus deep surgical anesthesia is desired. I keep my patients in as light anesthesia as I can so that uterine contractions keep the head and body placed.

Lacking Piper forceps, an ordinary Simpson forceps can be applied to the aftercoming head with a great deal of success in most cases.

DR. CARL HENRY DAVIS.—Some years ago I referred a multiparous patient, who had delivered easily the first time, to a younger man who was interested in external version. Finding that she had a breech presentation he attempted an external version in his office but did not succeed. Later he took her to the hospital and did an external version under ether anesthesia. Twenty-four hours later she delivered a stillborn infant which had been alive at the time the external version was performed.

In my earlier teaching experience we did not have the large clinical material which is now available, and we tried to save our breech deliveries for the students. It was, therefore, necessary for us to learn how to deliver the patient who had a breech presentation and, having learned, I, like many others, have ceased to fear the average breech delivery.

DR. WILLIAM R. NICHOLSON.—I am perfectly certain that the mortality that has been reported in breech delivery has been in most instances the result of undue interference. It is perfectly true that there are some cases of breech

takes a lot of experience and obstetric judgment to know when and how to interfere in the breech presentation, and the great majority of physicians doing obstetric work do not have that experience and judgment.

We have not thought well enough of the advantages of external version to practice it routinely at Temple. The more frequent use of forceps on the after-coming head and of perineotomy when there are indications of undue delay or difficulty, unquestionably are steps in the direction of lessened traumatism to the child, and therefore of lowered infant mortality. We should not lose sight of the fact, however, that more babies die from traumatism due to untimely interference, than from asphyxia from delay in delivery, or want of interference. We still believe in the wisdom of that early teaching at the Lying-In, and that, everything considered, it is safer to teach our undergraduates and internes to let the breech alone, and to keep hands off as long as possible, and wherever possible.

THE COLD PRESSOR TEST IN PREGNANCY*

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WE BEGAN to use the cold pressor test shortly after Hines and Brown described it. In a preliminary report published in 1935, we noted that pregnant individuals with a family history of hypertension usually gave more marked responses to the test than patients without such a history. Pre-eclamptic and eclamptic patients showed no uniform results with the test. Those patients who had hypertension, which was usually of the essential type, gave marked responses, both ante partum and post partum. It seemed that the test could be used to detect those patients who might subsequently in pregnancy develop hypertension or show evidence of vascular renal disease. The results of such a study are presented in this report.

Randall, Murray, and Mussey also applied the cold pressor test to pregnant patients. They found that 7 patients who were normal at the time of the test, but who gave an abnormal response, subsequently developed toxemia. They drew no conclusions but pointed out that 33 per cent of the patients who gave an abnormal test subsequently developed toxemia of pregnancy.

Briggs and Oertling, in 1937, reported their results of a study of 233 pregnant women. Only two hyperreactors were found, with no familial history of hypertension. No cases of toxemia that were of hypertensive origin occurred in the normal reactor group. Toxemia of nephritic origin did occur twice in the normal group. They concluded that their series was too small for definite conclusions, but it did seem that toxemia occurring upon a hypertensive background might be determined by means of a cold test.

TECHNIQUE

The subject is placed in a comfortable chair or in a semireclining position in bed. All extraneous noises and distractions are reduced to a minimum. A blood pressure cuff is applied to the arm and an arm band stethoscope is then adjusted to the cubital fossa.

If the patient cannot rest for an hour, blood pressure determinations are made at two- to three-minute intervals until a basal reading is obtained. The temperature of the water, which is 1° to 2° C., is obtained by having chipped ice in the water.

*Read before the Central Society for Clinical Research, November 5, 1937.

was a trained German midwife. On one occasion a woman in the delivery room seemed to be in active labor and the interne went to see what was happening. He saw the breech presenting and rushed for the Chief. The midwife gave one glance of scorn at the fleeing interne, placed her hand on the patient's fundus, and with one push the baby shot out upon the bed, while the nurse walked calmly on her way.

DR. JOHN C. HIRST.—In the last 3,100 deliveries at the Preston Retreat we had 124 breech deliveries resulting in 15 stillborn and 16 neonatal deaths, but we were able honestly to deduct 26 fatalities because of developmental defects, prematurity under twenty-eight weeks, and placenta previa, making a corrected mortality of 5 babies in 98 births, or slightly over 5 per cent. In the last 1,600 deliveries for which I have been responsible, we have made a real effort to do external version for each breech baby in a borderline pelvis. Among these cases we have had 53 breech presentations without a single viable death, only one decomposition and no cesarean sections.

DR. H. H. MUHLENBERG.—The country doctor may first of all emphasize the wisdom of not becoming terrified in the presence of a breech presentation, and giving the breech plenty of time, while carefully observing the fetal heart sounds. My second point is the great improvement in our statistics since we have routinely used aftercoming head forceps instead of making great pressure on the head from above.

DR. LIDA STEWART COGILL.—In a case where there is no existing disproportion between fetus and pelvis and no immediate need for delivery of the fetus, the patient should be permitted to deliver herself without any interference from the attending physician.

She may be assisted by means of the Kristeller method, which consists of placing the hands over the fundus and at the sides of the uterus, pushing downward during uterine contractions, thus aiding in the expulsion of the fetus and the preventing of extension of the upper extremities and head which so frequently follows when traction is made from below.

I think we are all agreed there is a greater amount of intracranial pressure present in an aftercoming head than in a cephalic presentation, therefore even with the use of Piper forceps we should deliver slowly in order to prevent a sudden increase in this pressure with its attending ill effects upon the fetus.

DR. ROY W. MOHLER.—May I call your attention to the fact that I said "complete" but not "deep" anesthesia. Anesthesia with gas and oxygen cannot be deep anesthesia. I also said that sometimes the extraction consists in only directing the baby through the mechanisms of labor. If you are going to anesthetize the patient you have to do something to direct the child through the pelvis in order to have a definite maneuver in labor.

DR. J. O. ARNOLD.—Dr. Mohler's report brought to mind my first and, as I look back now, most impressive lesson in the conduct of breech delivery. It was the first breech delivery I had ever seen and occurred at the Lying-In Hospital from which Dr. Mohler's report comes. The attending obstetrician and instructor, standing idly by while the child's unsupported breech protruded farther and farther with each pain, led to all kinds of wonderment on the part of the students. The attending doctor, noting our bewilderment, began to question us: "What should the attendant do now? What should be the position of his hands at this point in the conduct of the case?" When we had each attempted an answer, he said: "No, his hands should be as mine are now," and he stood apart from the delivery table, with his hands behind his back!

We have largely taught in our own clinic this hands-off, watchful-waiting policy, and from a review of our case records for a good many years, we have no reason to regret this cause. With all the improvements in methods, and the tendency to substitute artificial processes for the natural, the fact still remains that there is a decidedly higher fetal mortality with interference than without interference. It

patients took 20 as the maximal increase. Subsequently, Hines and Brown took 22 as the upper limit of normal in the nonpregnant. We have taken 29 as our upper limit of normal.

The large number of pregnant women who are hyperreactors requires consideration. We know that the blood pressure increases slightly as term is approached. The cause and mechanism are unknown. The blood and plasma volume and vascular bed are increased. The viscosity of the blood is decreased. The pulse rate is slightly increased. The nausea and vomiting, constipation, paroxysmal tachycardia, dermatographia, etc., of pregnancy are all thought to be due in part at least to sympathetic stimulation. This may also account for the high incidence of hyperreactors.

In the 0-19 group, one patient had toxemia and 2 others had normal pregnancies with the exception of the transient disturbances mentioned. Twenty-seven patients had normal pregnancies. The results in the 20 to 29 group are similar.

Fifteen patients out of 90 in the 30 and over group had definite evidence of toxemia and in 10 cases the hypertension was still present three months or longer after delivery. Thirteen patients had the transient findings listed.

It is worth noting that of the 152 patients tested, 90 gave a cold pressor rise of 30 mm. or more and 15 of these developed toxemia. Sixty-two patients gave a pressor rise of less than 30 and only 2 developed toxemia.

Four patients with a history of previous toxemia also gave a pressor rise of 30 or more but only 2 had a recurrence of toxemia.

The result of the test and subsequent symptoms and signs were compared with the total gain in weight. Certainly the majority (90 per cent) of the patients who gave a rise of 30 mm. or more, and either had toxemia or transient vascular renal symptoms, gained less than 15 kilograms of weight during pregnancy. Thus, these patients differ from those with pre-eclampsia who usually gain excessively or too rapidly or both.

Hines and Brown stress the importance of obtaining a basal blood pressure before testing the patient, and emphasize the value of comparing the "range" value with the "ceiling" value. They found that 98 per cent of the normal subjects, with normal range, had a ceiling of less than 145 mm. in the systolic pressure. Seventy-two per cent of the normal hyperreactors had a ceiling of more than 145 mm. systolic.

Several investigators have been unable to confirm the work of Hines and Brown. We believe that if basal pressures are obtained and if the blood pressures are taken every thirty to forty seconds during the immersion, certain patients will give marked increases in blood pressure and others little or no effect. Occasionally the blood pressure drops. To eliminate the personal factor, we have used the Tyco self-recording sphygmomanometer in a number of cases with results similar to those found with the auscultatory method. Furthermore, as we have previously reported, repeated ice water tests on the same day in 5 patients precipitated alarming vascular renal symptoms and signs.

The extended hand of the arm wearing the blood pressure cuff is immersed until the ice water reaches the wrist. Blood pressure readings are taken immediately and then every thirty seconds for two minutes when the hand is removed. The blood pressure is then taken at three-minute intervals for an additional fifteen minutes to note the time required for the blood pressure to return to the normal level.

One individual has performed most of our tests. A container, measuring 9 by 16 by 10 inches high, with an inclined screen 16 inches long at one end, was found more satisfactory than a pan. Ice chips were kept behind the screen, thus maintaining the temperature of the water at 1 to 2° C.

Over 400 pregnant women have been subjected on one or more occasions to the cold pressor test. One hundred fifty-two patients who were normal in all respects at the time of the test and who did not deliver for at least three months were selected for study. Our criteria for toxemia are as follows:

A systolic blood pressure of 140 or more on more than two days.

An extensive edema of the legs or generalized moderate edema with no recognizable cause except the pregnancy.

A proteinuria which is present daily for at least one week or which is noted on repeated tests for more than four weeks. The specimen of urine must be uncontaminated and there must be no urinary tract infection.

Usually more than one of the above are present.

Our data are listed in Table I. An abnormal vascular renal system may manifest itself during pregnancy as follows:

A. A transient rise of the systolic blood pressure to 140 mm. or more for one day. Proteinuria may frequently be associated with the hypertension.

B. A coincidental essential hypertension appearing early in pregnancy and becoming more severe as the pregnancy grows.

C. The exacerbation of an essential hypertension or of a chronic glomerulonephritis.

TABLE I. COLD PRESSOR TEST IN NORMAL PREGNANT WOMEN

TRANSIENT OR PERMANENT ABNORMALITIES OF THE VASCULAR RENAL SYSTEM	INCREASE IN SYSTOLIC MM. MERCURY		
	0-19	20-29	30 OR MORE
Hypertension		2	11
Hypertension and proteinuria			4
Hypertension, proteinuria, and edema			6
Hypertension and edema	1		3
Proteinuria	2	1	2
Edema		1	2
Total cases with abnormal vascular renal pathology	3	4	28
Total cases with normal pregnancy	27	28	62
Total	30	32	90
Patients with toxemia or permanent vascular renal disease	1	1	15

These vascular renal signs must be distinguished from the typical or true toxemia of pregnancy, i.e., pre-eclampsia.

Hines and Brown, in their first report, stated that the patient was a hyperreactor if the ice water test caused an increase in the systolic pressure of more than 15 mm. Randall and co-workers in pregnant

we are using them for differentiation of the toxemia and plan to apply both tests to a group of normal patients in early pregnancy and follow their subsequent course.

If a large number of tests confirm our findings, the cold pressor test will be of great value. First, it will enable us to select those patients who may develop toxemia and thus permit frequent observation and intensive study of these patients. The group of normal reactors need not be seen so frequently, thus decreasing the cost of prenatal care for this group. We, therefore, hope that other clinics will adopt it in order that a series of several thousand patients may be quickly collected.

SUMMARY

The cold pressor test was used in 152 normal pregnant women.

An increase in the systolic pressure of 30 mm. or more was considered abnormal.

Ninety patients were hyperreactors, 15 developed toxemia and an additional 13 had transient abnormal vascular renal signs.

Sixty-two patients gave a normal test. Only 2 developed toxemia and an additional 5 had transient signs.

The cold pressor test is compared with the pituitrin test.

An abnormal reaction of the former in a pregnant woman seems to indicate that she may develop a toxemia in which the hypertension is the predominant finding. An abnormal pituitrin reaction commonly occurs in patients with toxemia of the pre-eclamptic type.

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Among the minor surgical procedures Cotte mentions linear scarifications, superficial cauterization and local injections of anesthetic solutions or other liquids. In the latter class the best results have been obtained with injections of alcohol. Injections of oxygen and radioactive substances have also been used. Some physicians inject anesthetic solutions into the pudic nerves.

Among the more extensive surgical procedures, Cotte mentions vulvectomy. This operation is popular, but he is not impressed with its results. He discusses section of the subcutaneous and also the internal pudic nerves but personally favors resection of the presacral nerve. He performed two of these operations in men and three in women who had pruritus around the genital and anal regions. In this small series there were two complete and two partial successes and one failure. Cotte collected reports of 17 presacral nerve resections for pruritus. Of these patients 10 were completely, and 4 partially, relieved, and 3 cases were failures. The author prefers resection of the presacral nerve because it permits examination of the pelvic contents, carries little danger, and does not interfere with sexual function.

J. P. GREENHILL.

Chart 1 illustrates the results of the cold pressor test on a nonpregnant woman with family history of hypertension and the blood pressure curve of this same patient during pregnancy and the puerperium. A severe toxemia which we believe was primarily an essential hypertension was caused or precipitated by the pregnancy in a patient who had a predisposition to vascular disease. The blood pressure was still abnormal almost three years post partum, and we believe that it will not only never return to normal but will slowly increase. If other pregnancies occur, the rate of increase of the pressure will be hastened. We have similar curves for 14 other patients differing only in that the test was performed during pregnancy.

We, as well as several other physicians, have used the test in non-pregnant women as an aid in deciding whether or not it would be advisable for them either to become pregnant or have more pregnancies. If the patient has a border line blood pressure, 130 to 140 systolic, and gives a rise of 30 or more with the cold test, we advise against pregnancy. If the patient gives a history of previous toxemia and also is a hyper-reactor, we believe pregnancy is contraindicated. However, if the test is normal, the patient may become pregnant.

We certainly do not believe at this time that every patient, whether pregnant or not, whose systolic pressure increases 30 mm. or more after

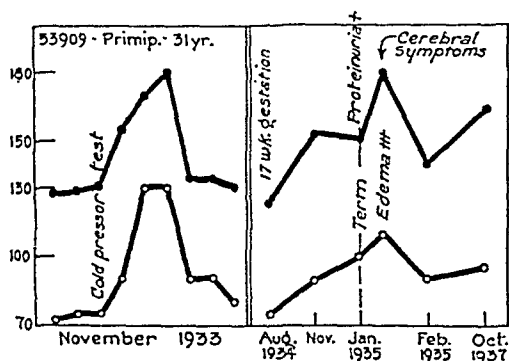


Chart 1.—Graph of cold pressor test and blood pressure curve of patient in subsequent pregnancy.

the cold test will either develop toxemia or should not become pregnant. But there is a definite relationship as indicated by our work as well as by that of the other two reports previously cited.

We have also been studying the effect of pituitrin on the blood pressure. Normal pregnant patients, after the subcutaneous injection of 1 to 2 minims of pituitrin, show an average increase in the systolic pressure of 11 mm. with a range of 0 to 20. Pre-eclamptic patients have an average increase of 51 and a range of 28 to 80 mm. Patients with essential hypertension or vascular renal disease have an average rise of 7.7 and a range of minus 10 to 18. Thus, pre-eclamptic patients give a marked response to pituitrin but a normal one to the cold pressor test. The patient with essential hypertension, with vascular renal disease or with family history of hypertension usually gives a marked response to the ice water test but a normal one to pituitrin. It seems that these tests may be used during pregnancy to differentiate the various types of toxemia and if used early in pregnancy they may indicate which patients may develop pre-eclampsia and which hypertension. At present

has been prepared. Whereas the Class I patients averaged only slightly over one day in the hospital prior to delivery, the severe Class III patients averaged 51.5 days. Although we have, of course, no rule or standard routine regarding the period of hospitalization, the figures in Chart 2 show almost a geometric progression, dependent on the grade of heart involvement.

Not only is it necessary that heart disease, if present, be recognized before or very early in a pregnancy, and adequate rest and hospitali-

CLASS	335 - TOTAL NUMBER OF CLASSIFIED CASES
1	1.4 DAYS
2 a	5.6 DAYS
2 b	17.2 DAYS
3	51.5 DAYS

Chart 2.—Average duration of hospitalization prior to delivery.

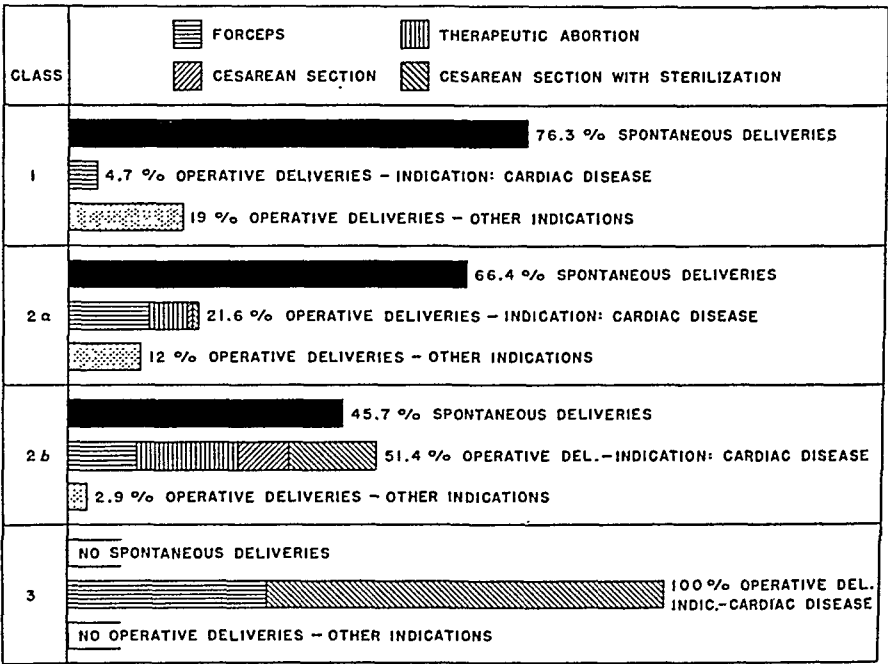


Chart 3.—Type of delivery in the various classes of cardiac disease.

zation during pregnancy be instituted but it is equally important that the patient receive the proper attention and treatment during parturition. We have found it exceedingly difficult, if not impossible, to follow any rule or routine. In Chart 3 an attempt is made to present a comprehensive view of our treatment during the delivery period. In each Class of cardiac patients, the types of delivery are divided in three groups, spontaneous, operative because of heart disease and operative on indications other than heart disease. Four further subdivisions of operative deliveries are shown, viz., forceps, therapeutic

HEART DISEASE COMPLICATING PREGNANCY

A STUDY OF 436 CASES

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A STUDY of 436 women, suffering from cardiac disease and observed in 493 pregnancies in the Lying-in Hospital (Woman's Clinic of the New York Hospital) during the five-year period ending Sept. 1, 1937, is the basis for this report. In a recent publication¹ Kuder and I described the role of a special ante-partum and post-partum cardiac clinic and the manner in which cardiac patients are treated in the Lying-in Hospital. In the present analysis emphasis is directed mainly to the important role heart disease plays in maternal mortality.

During the five-year period under review, cardiac disease occurred as a complication in 493 of 14,009 pregnancies on the Indoor Service of the Lying-in Hospital, an incidence of 3.5 per cent.

CLASS	335 - TOTAL NUMBER OF CLASSIFIED CASES
1	50.5 %
2a	37.3 %
2b	10.4 %
3	1.8 %

Chart 1.—Distribution of heart disease according to functional classification.

As stated elsewhere² we employ the functional classification of heart disease, formulated by the New York Heart Association. In 335 of the 436 patients studied, there was full agreement as to the exact classification, and we, therefore, believe that an analysis of this smaller group would be more accurate as to the relative frequency of the various classes of heart disease. In these 335 patients the distribution, according to the functional classification, is shown in Chart 1, which reveals 50.5 per cent of the cases of Class I, 37.3 per cent in Class IIa, 10.4 per cent in Class IIb, and 1.8 per cent in Class III. In other words, half of the patients belong in the mild Class I, whereas the other half fall in the potentially or actually dangerous groups (Classes IIa, IIb, and III).

In order to portray our attitude as to the value of early hospitalization prior to delivery in the several grades of heart disease, Chart 2

*Read at a meeting of the New York Obstetrical Society, December 14, 1937.

deaths on a basis of live births may be of use where full statistical data are not available, but is decidedly inaccurate as it is affected by the incidence of twins or other types of multiple births and actually utilizes the fetal mortality rate to express maternal mortality.

Approximately one-fourth of our deaths were due to hemorrhage (ante partum and post partum), and 15 per cent were due to infections. Pneumonia accounted for 13.2 per cent, while cardiac disease is the fourth most important cause of maternal mortality, accounting for 8.7 per cent of the deaths, and followed by toxemias with only 6.5 per cent. Furthermore, it is to be noted that the 3 maternal deaths, or 6.5 per cent of the maternal mortality, due to toxemias, were all caused by acute yellow atrophy and chronic nephritis. In this chart, therefore, infection is no longer the major cause of maternal mortality and the toxemias account for a relatively small percentage of the death rate, and even then it is necessary to include under "tox-

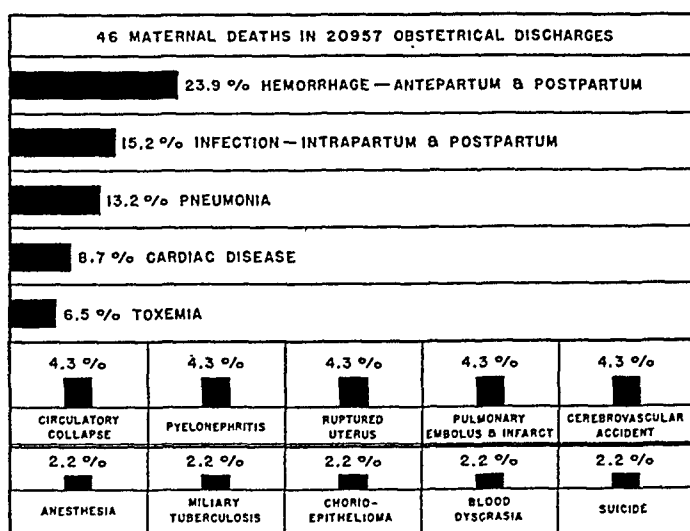


Chart 4.—The causes of maternal mortality.

emia," chronic nephritis. I have elsewhere⁴ discussed in detail the factors responsible for the reduction in maternal mortality in both these groups, infection and toxemia. Here I wish to emphasize the important roles played by pneumonia and cardiac disease as factors in maternal mortality. Hemorrhage, both ante partum and post partum, is receiving particular attention in many maternity hospitals and in our clinic by Pastore and his co-workers, who are studying the problem of blood loss in relation to infection and the toxemias.

To repeat, cardiac disease, as shown in Chart 4, is the fourth most important cause of our maternal deaths and is a greater factor, in the total maternal death rate, than the toxemias of pregnancy.

Of the 493 pregnancies complicated by cardiac disease, 475 occurred in registered and 18 in unregistered patients. Chart 5 shows that in each of the two groups, registered and unregistered, there were two maternal deaths, giving a death rate of 0.42 per cent in the registered and 11.11 per cent in the unregistered patients. It will be noted that

abortion, cesarean section, and cesarean section with sterilization. Spontaneous delivery occurred in 76.3 per cent of Class I, 66.4 per cent of Class IIa, 45.7 per cent of Class IIb, and zero per cent of Class III cardiac patients. On the other hand, the operative deliveries performed because of heart disease form 4.7, 21.6, 51.4, and 100 per cent, respectively, in the four classes. The third set of figures, namely those for operative deliveries on indications other than cardiac disease, are inserted to complete the figures and so enable one to compute the correct percentages for the several groups. Although, as stated above, no rule of treatment is followed in our clinic, it is noteworthy how the number of operative deliveries, because of heart disease, proceeds from 4.7 per cent in Class I to 100 per cent in Class III.

Therapeutic abortion for heart disease was done in only Classes IIa and IIb. That this operation was not performed in Classes I and III, is presumably due to the fact that in the former the heart affection was not deemed sufficient reason for interruption of a pregnancy, while in the latter the patients were too ill or too far advanced in pregnancy to make interruption the procedure of choice.

It will be noted that whenever cesarean section was performed in Class III cardiac patients it was on the cardiac indication and was always accompanied by sterilization. On the other hand, cesarean section constituted only about half of the operations, based on cardiac indication, in Class IIb, and again, in only slightly over half of these cesarean sections was sterilization performed. Expressed differently, pregnant patients with cardiac decompensation or Class III heart disease complication are invariably treated with long periods of hospitalization followed by forceps delivery or cesarean section and sterilization; while those with Class IIb heart disease are similarly hospitalized, but usually for shorter periods, and are delivered either by forceps or cesarean section, with or without sterilization. It must, of course, be evident that the decision as to type of delivery, as well as to the question of sterilization, rests on many factors and is an individual matter in each patient.

It is our very definite conclusion¹ that pregnancy is a strain on the heart and that labor adds still more to this load; furthermore, that where the heart is already diseased, this strain of pregnancy and labor may be sufficient to either markedly aggravate the cardiac condition or produce actual failure resulting in death. Analysis of the maternal mortality in the Lying-in Hospital has brought this conclusion particularly to our attention. In Chart 4 are given the causes of our maternal mortality. During the five-year period studied we had 46 maternal deaths in 20,957 obstetric discharges, an uncorrected mortality of 2.18 per 1,000 obstetric discharges. This incidence may be expressed as 2.62 per 1,000 full-term and premature deliveries, or 2.69 per 1,000 live births or 2.43 per 1,000 pregnancies. We believe, as stated in an earlier publication,³ that the last figure is the most accurate expression of maternal mortality, as it takes into account abortions, ectopic pregnancies and patients dying undelivered and is not vitiated by multiple births. The method of expressing maternal

5.38 in cardiac and 5.46 in clinic patients, and an infantile mortality of 3.71 per cent in cardiac and 4.12 in the total clinic patient group. From these figures we may conclude that cardiac disease in the mother does not increase the loss in offspring by increasing either the rate of spontaneous abortion or infantile mortality. The only way in which cardiac disease may effect infant loss would be indirectly, through the number of therapeutic abortions performed because of heart disease.

In conclusion, I wish to emphasize the value and need of a special cardiac clinic in every obstetric service, the necessity of an adequate workable classification of heart disease, such as the functional one of the New York Heart Association, the urgent need of early registration, with a doctor or clinic, of every woman who becomes pregnant, the importance of a thorough heart examination at this first registration, the value of rest and hospitalization for patients suffering from heart disease and the importance of the proper method of delivery for each patient.

CONCLUSIONS

1. In a five-year study, comprising 20,957 obstetric discharges, from our indoor and outdoor services, the incidence of heart disease was 3.5 per cent of the total number of pregnancies.

2. The distribution of the cardiac patients, according to the functional classification, was 50.5 per cent in Class I, 37.3 per cent in Class IIa, 10.4 per cent in Class IIb, and 1.8 per cent in Class III.

3. The duration of hospitalization, prior to delivery averaged 1.4 days for Class I, 5.6 for Class IIa, 17.2 for Class IIb, and 51.5 days for Class III patients.

4. In addition to rest and long periods of hospitalization, the treatment as to delivery is most important.

5. Therapeutic abortion for heart disease was performed in only Classes IIa and IIb patients, and amounted to 2.55 per cent.

6. Forceps delivery upon full dilatation of the cervix is a great aid in the handling of many cardiac patients. This means of delivery, because of heart disease, was performed in 4.7 per cent of Class I patients, 13.6 in Class IIa, 11.42 in Class IIb, and 33.3 in Class III.

7. Cesarean section, under proper anesthesia, preferably open drop ether or local, has a definite role in the treatment of heart disease. In our series of cases cesarean section, on the indication of heart disease was performed in 1.6 per cent of Class IIa, 22.9 of Class IIb, and 66.7 per cent of Class III patients. In Class IIa about 50 per cent of the cesarean section operations were accompanied by sterilization, in Class IIb patients 62.5 per cent and in Class III patients 100 per cent of the cesarean sections were followed by tubal sterilization.

8. During the five-year period, our total uncorrected maternal mortality in the 20,957 obstetric discharges from the indoor and outdoor services was 2.19 per 1,000 discharges, or 2.62 per 1,000 deliveries, or 2.43 per 1,000 pregnancies or 2.69 per 1,000 live births. The method of expressing mortality, on the basis of the number of maternal deaths per 1,000 women who become pregnant, appears to us to be the only

the maternal mortality in the unregistered patients is over 26 times that in the registered group. Although other factors come into play, such as the fact that seriously ill patients are generally brought to a hospital, the difference in these rates is exceedingly striking, and bespeaks the value of early recognition of the disease and proper hospitalization.

What is the effect on fetal mortality of heart disease in the mother? In Chart 6 we have compared the total product of conception loss in our cardiac patients admitted to the Lying-in Hospital during the

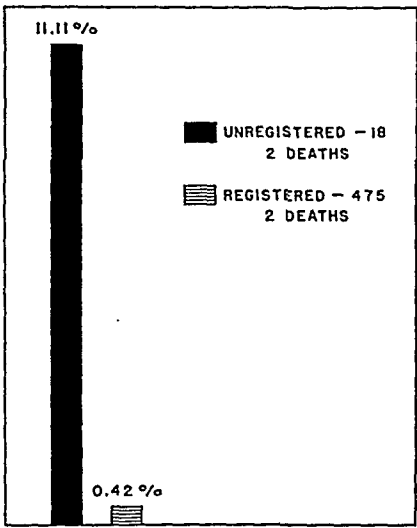


Chart 5.—Maternal mortality in registered and unregistered patients.

C A R D I A C P A T I E N T S			
I N F A N T I L E M O R T A L I T Y	A B O R T I O N S		T O T A L
	N O N - T H E R A P E U T I C	T H E R A P E U T I C	
3.71 %	5.38 %	2.55 %	11.64 %

I N F A N T I L E M O R T A L I T Y	A B O R T I O N S		T O T A L
	N O N - T H E R A P E U T I C	T H E R .	
4.12 %	5.46 %	.79 %	10.37 %

| T O T A L C L I N I C P A T I E N T S | | | |

Chart 6.—Incidence of infantile mortality and abortion in cardiac disease.

five-year period. This loss in offsprings is composed of abortions, both spontaneous and induced, whether criminal or therapeutic, and infantile mortality. Again infantile mortality includes premature, full-term, and neonatal deaths occurring within two weeks after delivery. The percentage loss in each group is calculated on the basis of the total possible live babies, which include all pregnancies, whatever the duration, as well as the multiple births. On such a basis the total offspring loss in the cardiac group is 11.64 per cent compared with 10.37 per cent in the clinic population. These totals, when analyzed further, show a therapeutic abortion loss of 2.55 in cardiac and 0.79 per cent in clinic patients, nontherapeutic abortion loss of

her life as the direct outcome of childbirth, yet we shrug our shoulders in smug complacency as the unborn and newborn infants run up a mortality of 42 per thousand or 21 times that of the mother. To me it seems a sad commentary on our obstetric teaching and practice when we must admit that 1 out of every 10 pregnancies will result in a failure; that 1 woman out of every 38 who passes the period of viability will have a dead born baby; that 1 woman out of every 68 will give birth to a live baby only to see it die during the first two weeks of its life, and, combining both the stillbirths and neonatal deaths, that every woman who passes the period of viability has 1 chance in 24 of being discharged from the hospital without her baby.

In 1918 Edgar, in a review of 519 stillbirths, pointed out that the great lesson to be learned from such a study was the necessity for adequate prenatal care. In addition he found that prolonged labor, especially when associated with dystocia, also toxemia, eclampsia, and syphilis all took their toll of infant life and could be avoided if recognized early and treated properly. He pointed out, as Bundesen and his associates have done recently, the necessity of a complete autopsy study in dealing with the question of stillbirth and regarded the premature baby as a hopeless problem.

At the end of the same year Davis, in his address before the American Association for the Study and Prevention of Infant Mortality, said "When the world is passing through a crisis of reorganization and nations are torn down and built anew, the individual fiber of a nation becomes of the greatest importance. The real test of strength is now to be made, and whatever balance may be achieved, the preservation of that balance and the hopes of the world will depend on the individual citizens of each state. The coming generation then will decide the power and pulse of this nation in the great international competition which is inevitable. More than ever are the life and health of the infant of today the insurance and guarantee of national strength for the coming generation." With the uncertain condition of world affairs today and the decline in our birth rate, it seems of utmost importance for us to recognize that these words are equally as prophetic today as they were at the close of the great war twenty years ago.

During the three years 1934 to 1936 inclusive, 6,844 pregnancies were terminated on the Obstetric Service of the Jewish Hospital of Brooklyn. The end results are shown in Table I.

TABLE I

Mothers delivered	6,844
Twin pregnancy	79
Triplet pregnancy (1)	2
Total possible babies	6,925
Abortions	309
Viable babies	6,616
Stillbirths	175
Live births	6,441
Neonatal deaths	97
Discharged live babies	6,344

accurate one, as it includes all pregnancies, of whatever duration, and does not utilize other variables, such as fetal death rate or the incidence of multiple pregnancies.

9. Cardiac disease was responsible for 8.7 per cent of our total uncorrected maternal mortality, being the fourth largest factor in this death rate.

10. The maternal mortality in unregistered cardiac patients was 26 times that in those who registered in our clinic during the prenatal period.

11. Cardiac disease in the mother does not directly effect the loss in offsprings by increasing the spontaneous abortion rate, and/or the infantile mortality rate, comprising premature, full-term and neonatal deaths. This offspring loss, nontherapeutic abortions plus infantile deaths, was 9.09 in our cardiac patients and 9.58 in our total clinic population.

12. The early recognition of heart disease, rest and long periods of hospitalization, special cardiac clinics in maternity services and the proper type of delivery are among the important factors to reduce maternal mortality caused by cardiac disease.

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THE PROBLEM OF INFANT MORTALITY*

JOSHUA RONSHEIM, M.D., BROOKLYN, N. Y.

FOR some time tremendous effort has been put forth in this and other civilized countries for the purpose of reducing deaths in childbirth. National, state, and local societies have organized special groups to spread the gospel of prenatal care and better care for the mother in labor and in the puerperium. A wealth of literature has been devoted to the subject, some of which has been quoted in the newspapers, firing the imagination of the public. The doctors of any given community have been literally hounded by these special groups seeking to spur them to greater effort for better care with but one object in mind—to bring the death rate in childbirth to an irreducible minimum. Throughout this entire campaign little has been said or done in an attempt to improve the possibilities for the unborn and newborn babies; they have virtually become medicine's "forgotten men." I am not unmindful of the fact that the maternal death rate for the entire country is high; I do know, however, that in the larger maternity clinics it rarely exceeds two per thousand. While we are greatly perturbed by the knowledge that, even in the best institutions, one woman in every five hundred will sacrifice

*Read at a meeting of the Brooklyn Gynecological Society, March 4, 1938, by Dr. William Epstein, Resident obstetrician, Jewish Hospital.

TABLE III

STILLBIRTHS		DEAD ON ADMISSION	
Dead on admission	75	Cause undetermined	37
Died before delivery in hospital	8	Maternal nephritis	4
Died in first stage labor	58	Placenta previa	1
Died in second stage labor	34	Syphilis	7
		One of twins	1
		Postmaturity	1
		Maternal cardiac	1
		Ablatio placentae	10
		Monstrosity	2
		Toxemia	8
		Prolapsed cord	1
		Strangulation of cord	1
		Trauma	1

All of these cases were carefully studied; yet in half of them we were unable to arrive at any cause of death either in the mother or in the fetus. As a great many of these fetuses are thoroughly autolyzed, necropsy is of no value other than the gross examination, microscopic investigation being impossible. Nevertheless and in spite of the difficulties that we may encounter, I believe it is safe to say that had these patients had proper prenatal care, probably more than half could have been carried to a successful issue. Syphilis, nephritis, and toxemia are alone responsible for 25 per cent of all the above stillborn babies.

Eight cases of a large number admitted to the hospital for observation and treatment in the ante-partum period suffered death of the fetus in utero. Six of these had toxemia of pregnancy, one had chronic nephritis, and one had a sudden ablatio. It is difficult to judge these cases. Premature babies of such mothers are usually poor risks, yet with proper prenatal care the outlook might have been better. Had induction of labor been performed before the death of the fetus occurred, the end result might very likely have been the same. However, the number of cases is too small to be an important factor.

TABLE IV

DEATH IN FIRST STAGE OF LABOR		DEATH IN SECOND STAGE OF LABOR		NEONATAL DEATH	
Prolonged first stage	17	Birth trauma	15	Prematurity	41
Undetermined	10	Prolonged second stage	5	Birth trauma	18
Monstrosity	6	Monstrosity	5	Monstrosity	15
Prolapsed cord	6	Prolapsed cord	4	Congenital disease	12
Ablatio placentae	5	Prematurity	2	Septicemia	4
Maternal nephritis	3	Placenta previa	2	Hemorrhagic disease	2
Eclampsia	3	Erythroblastosis	1	Pneumonia	1
Toxemia	2		—	Umbilical hemorrhage	1
True knot in cord	2		34	Erysipelas	1
Oligohydramnios	1			Undetermined	2
Placenta previa	1				—
Prematurity	1				97
Amniotic infection	1				
	—				
	58				

It is in this large group of stillbirths and neonatal deaths, and especially among the stillbirths occurring during labor, that the field of

Between the number of mothers admitted and the number of live babies discharged, there is a difference of exactly 500; allowing for multiple pregnancies this means that more than 500 mothers left the hospital after having been pregnant for periods varying from its inception to term with nothing to show for the suffering entailed by the pregnancy and labor. Who can measure the mental anguish endured by these women or the pelvic disorders and sterility that follow in the wake of poorly timed and badly performed operative deliveries?

A comparative study of the results obtained in several other institutions during the same three years is shown in Table II.

TABLE II

	JEWISH	HAGUE	SLOANE	LICH	LYING-IN
Abortions	4.46%	2.53%	7.55%	2.85%	6.61%
Stillbirths	2.53	2.38	1.59	2.55	2.42
Neonatal deaths	1.40	2.65	2.01	1.39	1.48
Total	8.39	7.56	11.15	6.79	10.51
Total stillbirth and neonatal death	3.93	5.03	3.60	3.94	3.90
Total cases	6,844	15,895	7,405	3,887	8,512

We observe a marked difference in the percentages of abortions and a striking similarity in the percentages of stillbirths and neonatal deaths despite the great differences in the totals of cases handled. The larger percentage of neonatal deaths at one institution probably will be explained by the inclusion in this group of nonviable pregnancies that have lived for a short time. It is my custom to classify every pregnancy which terminates before the twenty-eighth week of intrauterine life or which results in a fetus of less than 1,320 gm. as an abortion.

In an attempt to arrive at some idea as to what proportion of these babies might be saved, the abortions, stillbirths, and neonatal deaths were tabulated according to cause. Naturally, not all these pregnancies can be saved; in spite of all our efforts in this direction we will still have to face the problem of induced abortion; we probably will never solve the enigma of congenital malformation and congenital disease of hidden origin, while some of our premature infants will continue to die in spite of our best efforts to save them.

ABORTIONS

Spontaneous and induced	249
Therapeutic	43
Missed	17

While it is probable that some of the spontaneous and missed abortions will be saved by hormone and other therapy and that more careful study of some cases will result in the lowering of the number of therapeutic abortions, we are, nevertheless, in no position to make any definite statement as to how many of these could have been avoided. Prevention of spontaneous abortion may very likely lead to an increase of missed abortions. The field for prevention of infant mortality lies almost exclusively among the viable infants.

terminated before the twenty-eighth week of intrauterine gestation and resulted in a fetus of less than 1,320 gm. was classified as an early abortion (if before the fifteenth week) or a late abortion. A baby born between the twenty-eighth and thirty-eighth weeks and weighing up to 2,400 gm. was classified as a premature infant; all others were classified as full term. In doubtful cases the length of the fetus was considered. If the baby weighed over 4,400 gm. and the intrauterine gestation period was over forty-three weeks, the baby should be included in the group of postmaturity. This method of grouping follows rather closely that promulgated by Adair.

2. *The Teaching and Performing of Better Obstetrics.*—It is not enough that the student and intern learn normal obstetrics; he must be taught to recognize the deviations from the normal and then, if he regard himself as not capable of dealing with the abnormality, his immediate concern should be the presence of competent assistance. Hospitals in which obstetrics is practiced should have a capable obstetrician available at all times for the guidance of those dealing with abnormalities. Those institutions with sufficient clinical material should maintain a resident staff, thus providing the competent obstetricians of the future. When labor is prolonged or dystocia is present consultation should be imperative; in this way unnecessary or wrong interference and unnecessary delay in the performing of operative delivery may be prevented. In spite of everything that we may attempt along the lines of prevention the untrained attendant will ever undertake that which he is incompetent to do; this problem will only be solved when the hospital authorities demand proof of a man's obstetric ability ere he be permitted to practice obstetrics in the institution.

3. *The Economic Problem.*—Until we make it possible for marriage to occur at an earlier age or, being married, make it possible for the young couple to have the first baby at an early period in the marriage, the elderly primipara will continue to be a source of danger. Some interesting facts are brought to light when we divide the patients into private and general service groups. Less than 3 per cent of all private patients have their first baby before passing the twentieth year; among the general service patients the figure jumps to 31 per cent. Only 5 per cent of the general service patients have their first baby after the thirtieth year as compared to 12 per cent for the private patients. *ALL* the patients who gave birth to the first baby after thirty-five years of age were private patients. If bringing forth children late in life predisposes to the possibility of monstrosity, it is plain that this source of infant mortality will be reduced if childbearing occurs in earlier life; at the same time the dangers to the baby from increased size, rigid maternal soft parts, and toxemia will be reduced.

4. *Prenatal Care.*—The importance of prenatal care must be brought home to those who do not seek it and better prenatal care must be given to those who do seek it. It is not enough that the patient be seen at stated intervals; careful interrogation and thorough investigation will frequently disclose conditions which threaten the unborn child. Syphilis,

prevention broadens out. The deaths from birth trauma and prolonged labor constitute 30 per cent of the total and are definitely avoidable; they stand as a serious blot on our obstetric record. Many premature babies will be given a better chance if the rigid perineum is incised thus avoiding prolonged pressure on a soft head. However, we must not permit the dissemination of the idea that infant mortality can be eliminated completely. Nor should all of this mortality be placed on the obstetrician's threshold. Many abortions are self-induced and, no matter what we may do, some pregnant women will continue to disregard prenatal care even when confronted with threatening symptoms. Therapeutic abortion must be done occasionally; congenital malformation will continue to take its toll, and premature babies will sometimes fail to make the grade. Finally, we must never lose sight of the fact that every now and then the baby must be sacrificed so that the mother may live.

Investigation of the necropsy protocols reveals the fact that 168 of these 272 deaths (61.7 per cent) found their way to the autopsy table; of these only 65 gave positive information as to the cause of death. In the group which gave negative findings, there are included those whose mothers had complications such as toxemia, ablatio placentae, placenta previa, etc., also many premature infants. Then, too, many macerated fetuses had undergone such autolysis that microscopic evidence of any value could not be obtained although, grossly, nothing was found to explain the death.

TABLE V. NECROPSY RESULTS

Negative findings	103
Intracranial hemorrhage	24
Monstrosity	16
Syphilis	7
Erythroblastosis	5
Hemorrhagic disease	4
Aspiration asphyxia	4
Pneumonia	2
Rupture of trachea	1
Hemorrhage from cord	1
Pemphigus	1

What, then, can we as obstetricians do toward bringing this infant mortality to an irreducible minimum? To my mind our efforts must be directed along the following lines:

1. *Terminology.*—The question of what constitutes a stillbirth, a live birth, and a neonatal death is, apparently, a matter of choice for any given community, as a glance at the map in the article by Williams will show. Right here in New York City our Department of Health demands a stillbirth certificate for every pregnancy that does not produce a live child irrespective of the duration of the intrauterine gestation period. Likewise, every fetus that has given evidence of being alive at birth must be reported as a live birth and neonatal death, also irrespective of viability. I am quite satisfied that there must be very definite reasons for all this, yet it is obvious that such statistics only give a distorted picture because they include early and late abortions among the stillbirths and neonatal death figures. In this study all pregnancies that

DR. GEORGE H. DAVIS.—It seems to me that neonatal care offers the greatest possibilities for reducing infant mortality. In the Hospital in which I work we have been able materially to reduce our neonatal deaths by turning our babies, private as well as ward, over to the pediatric department at birth. It may be questioned whether the pediatrician is properly trained to take care of newborn babies. His basic training, however, equips him to acquire the additional experience necessary for newborn care very quickly. Certainly in our institution his care of the newborn, particularly in premature and immature babies, has been more thorough and superior to the care given by the busy obstetrician.

DR. HARRY W. MAYES.—In our great enthusiasm to reduce maternal mortality and to check up so carefully on each death, we have seriously neglected the newborn infant. When we consider that 95 per cent of all the babies born in our city hospitals, and about 50 per cent of those delivered in the private hospitals, are under the care of residents, interns, and students, and when we realize that these cases are supervised by the attending staff only when some abnormality is noted, then perhaps we should be encouraged when we find that we have a fetal mortality of only 50 or 60 per thousand births.

Cesarean sections, versions, and forceps deliveries done with little or no indication by the untrained attendant, take their toll among the babies as well as the mothers. This may be used as one argument in favor of the midwife. The promiscuous use of drugs in the induction of labor and of analgesics and anesthetics during labor and delivery, while useful in the hand of the experienced obstetrician, may be abused by the overenthusiastic intern or resident.

I am still old fashioned enough to believe also that the mother's milk was made for the baby and that the milk contains some ingredients whether they be hormones, antitoxins, or what-not, which are vitally essential in protecting the baby from infection and preparing its alimentary canal for the functions required of it. If the baby is never taken to the mother's breast, but fed only from sterilized bottles with sterilized formulas, how is it going to establish the proper intestinal flora which is so essential in the processes of digestion? Breast feeding is a definite aid in getting the baby through those hazardous first few weeks of life.

DR. WILLIAM EPSTEIN.—In answer to Dr. Maisel's question, I may say that the types of delivery have not been separately tabulated by Dr. Ronsheim, the infant deaths due to breech delivery being included under birth trauma.

Kenny, Meave: Remote Effects of Puerperal Sepsis, *Lancet* 1: 14, 1937.

This study evaluates the remote ill effects of puerperal infection in 100 unselected women. An allowance was made for the psychic factors resulting from the stress and strain of pregnancy, labor and return home to the old routine with new responsibilities and the influence of the rest, care, and better living conditions of the hospital where these patients were treated.

The five groups investigated and their respective totals are: acute septic endometritis without complications, 22; pelvic cellulitis with or without thrombosis, 36; peritonitis, 14; septicemia, 19; and endometritis with complications elsewhere, 9.

The following summaries include the salient features found: Some psychical and physical debility is a common postnatal finding for those of low economic level. Complete restoration to normal health may be expected for a large majority recovering from severe puerperal infection. Rheumatoid arthritis and mitral valvular disease and some other morbid conditions appear to be closely related to puerperal infection.

Sterility is a prominent sequel to puerperal infection.

A notable number of cases revealed no gross lesion of the pelvic organs. Only 13 of the 100 women had tubal masses, uterine displacements, cervicitis, or vaginitis.

H. CLOSE HESSELTINE.

toxemia, nephritis, diabetes, and disproportion will continue their high percentage of ante-partum and intra-partum fetal death unless we avail ourselves of the assistance of those individuals who have special training to offer. Special clinics within the prenatal clinic will safeguard the lives of many unborn children. At these special clinics the cardiologist, roentgenologist, syphilographer and others will give their advice and counsel to the obstetrician. Social service workers, visiting nurses, and maternity centers should cooperate in getting the patients to the prenatal clinics and in looking after the families while the mothers are in the hospital.

5. *Immediate and Late Puerperal Care.*—Even though there be no bleeding during labor or immediately thereafter, inspection of the cervix will frequently reveal extensive laceration which should be repaired. Proper exercises in the lying-in period will aid the involution of the uterus and help to prevent the retroversion and endometritis resulting therefrom. Later, cervical erosions should be destroyed. By these means many subsequent abortions and some cases of placenta previa will undoubtedly be avoided.

6. *The Care of the Newborn.*—Many premature infants can be saved by proper handling and feeding. Hemorrhagic disease of the newborn will become a memory when we recognize the value of injections of whole blood at the time of birth in those infants that show any cyanosis. The early diagnosis and treatment of erythroblastosis and congenital syphilis are essential if we wish to save those so afflicted. Last, mortality from birth trauma will be reduced tremendously just as soon as the practice of obstetrics is placed on a proper basis.

205 HICKS STREET

DISCUSSION

DR. WILLIAM SIDNEY SMITH.—A recent article in *Harper's Magazine*, entitled "Shall We Subsidize Our Children?" takes the view that parents on both sides of the house should subsidize their children in order that they might be able to marry young and bring forth children early. The author of this article and Dr. Ronsheim have many economic ideas in common.

I also was interested in the topic of who should care for the newborn infant, the pediatrician or the obstetrician. I have a strong feeling that the mother and the baby should be treated as an entity. The pediatrician can teach us much about the care of the newborn babe and the obstetrician can certainly teach the pediatrician much about the mother's condition, and about her labor. The care of mother and baby will be very much better if the pediatrician and the obstetrician work hand in hand.

DR. FREDERICK J. MAISEL.—I did not notice a separate tabulation of breech stillbirths in Dr. Ronsheim's tables. We recently studied our stillbirths at St. John's Hospital and while our general stillbirth incidence was comparable to that in Dr. Ronsheim's report, there was a high proportion of stillbirths due to breech presentation.

DR. JACQUES LISWOOD.—At the Israel-Zion Hospital we formerly had the pediatric staff see only service cases. We were amazed to discover that many of those service babies seemed to do better than some of the private cases. At the present time the pediatric staff goes into the nursery every morning to see if the nurse in charge reports any babies with abnormalities.

Hospital prenatal clinic, and 6,042 mothers were referred from other sources. There were 798 stillbirths and neonatal deaths, a gross mortality rate of 4.9 per cent. This figure includes all infant deaths occurring in gestations of five months or over. In compiling the corrected infant mortality all infants weighing less than 1,500 gm. were considered previable and were deducted. Also, cases in which syphilis and congenital malformations were the sole cause of death were deducted. All other cases were included in the corrected infant mortality, if the fetal heart tones were heard at least once after admission, and if the birth weight was over 1,500 gm. Thus, 509 cases were excluded, leaving a total of 289 deaths, or a corrected infant mortality rate of 1.78 per cent. Of the 509 cases not included, 285 weighed under 1,500 gm. at birth and 224 weighed over 1,500 gm. Two hundred and eighty-four were dead on admission to the Hospital, 50 died of congenital anomalies, 63 died of syphilis, and 102 infants were alive at birth, but died early in the neonatal period because of prematurity (under 1,500 gm.).

In the entire series of 16,242 births, 14,861 were spontaneous, inclusive of 604 breech deliveries which were assisted manually after spontaneous delivery to the umbilicus; 1,381 deliveries were operative, inclusive of 196 bag insertions, a total operative incidence of 8.6 per cent. Among the 14,861 spontaneous deliveries, there were 602 infant deaths, a gross mortality rate of 4 per cent, whereas among the 1,381 operative cases, 196 infants died, a gross infant operative mortality rate of 14 per cent.

Table I represents the results in 634 breech presentations.

TABLE I. BREECH PRESENTATIONS

DELIVERIES		TOTAL DEATHS	GROSS MORTALITY RATE	CORRECTED MORTALITY	CORRECTED MORTALITY RATE
Spontaneous breech	604	47	7.8%	23	3.8%
Breech extraction	30	6	20.0%	5	16.0%
Total breech deliveries	634	53	8.3%	28	4.4%

The 604 cases classed as spontaneous breech deliveries include all cases in which the breech was allowed to deliver spontaneously to the umbilicus and assistance rendered only when necessary; whereas those cases listed as breech extractions refer to cases in which interference was instituted before the umbilicus was visible for a definite reason, usually because of fetal distress. Of the 24 cases excluded, 11 were dead upon admission, 10 weighed under 1,500 gm. at birth and 4 died as a result of congenital anomalies. The advantage of conservative management of breech presentations is indicated in Table I.

An analysis of Table II reveals a gross infant mortality rate in cesarean sections of 15.2 per cent and a corrected infant mortality rate of 8.3 per cent. This high cesarean section infant mortality necessitates further investigation and is classified in Table III as to indication for abdominal delivery.

In this series of 44 infant deaths that were delivered by cesarean section, 15 infants were dead on admission to the hospital. The operation was performed in 10 of these patients for ablatio placentae, in 2 cases for placenta previa totalis in primipara and in 3 for ruptured uteri. Of the remaining 29 cases, three infants weighed under 1,000 gm., the indications for cesarean section being impending eclampsia, 2 cases and ablatio placentae, 1 case. Four infants weighed between

INFANT MORTALITY AT THE COOK COUNTY HOSPITAL AMONG SIXTEEN THOUSAND DELIVERIES*

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IN THE past twenty-five years, there has been a definite improvement in the death rate of infants during the first year of life. The mortality at birth and during the neonatal period has remained practically unchanged. As a result of improved prenatal care and supervision some reduction in the neonatal death rate has been achieved. There are still many intrapartum and neonatal deaths due to ill-timed, ill-chosen, and unnecessary operative procedures. Unfortunately there has been in the recent literature an indication of a tendency in the direction of more active operative interference in labor, the wisdom of which can be seriously called into question. A statistical survey of the infant mortality at the Cook County Hospital was made to analyze the results of what may be regarded as a conservative policy in this department with respect to operative procedures including delivery by cesarean section. True conservatism consists as much in the performance of operations properly selected and performed as it does in a well-considered policy of allowing the patient to deliver spontaneously. In a study of infant mortality the question as to whether too many or too few operative deliveries are performed can only be answered by a consideration of the number of infants lost who could have been saved by some operative procedure without undue risk to the mother.

Normal deliveries are conducted by the internes under the supervision of the resident physician. Analgesias are rarely used because of the expense involved and the limitation of personnel. Inhalation anesthesia is used only when operative procedures require it. Local infiltration with $\frac{1}{2}$ per cent novocaine is used for the performance of episiotomy and repair of lacerations. Frequently, in selected cases, pudendal nerve block is resorted to, for the performance of simple operative procedures.

As in all large charity institutions, Cook County Hospital accepts patients who have had no prenatal care; patients who have been referred from clinics other than that associated with the Hospital, because of complications of pregnancy or labor; and many patients who have been under the care of private physicians or midwives and are admitted to the Hospital as emergencies.

This survey covers a four-year period, 1933 to 1936 inclusive, during which time 16,242 babies were delivered, including 184 sets of twins. Of the 16,058 mothers delivered, 10,016 attended the Cook County

*Presented at a meeting of the Chicago Gynecological Society, December 17, 1937.

section, but in 6 cases delivery was accomplished by decapitation, 4 of which were admitted to the hospital as neglected transverse presentations.

The Voorhees' bag was inserted 196 times, the indications follow:

Induction of labor for toxemia	126
Application of bag for cervical dystocia	19
Placenta previa	28
Transverse presentation	9
Ablatio placentae	9
Prolapsed cord	8

There were 40 infant deaths following the use of the bag. Twelve of these deaths occurred following the induction of labor for toxemia and 16 deaths occurred in cases of placenta previa in which bag insertion was the treatment of choice. This operative procedure was successful in preventing the deaths of the infants in 3 cases of prolapsed cord but failed in 5 other cases. In 12 of the 40 infant deaths, death was due to prolapsed cords following the expulsion of the bag with incomplete dilatation of the cervix. When the use of the bag is indicated because of important maternal complications, the danger to the infant may be regarded as a matter of secondary importance.

Table IV presents the infant mortality as to causation not attributable directly to obstetric operative procedure, and comparing these contributing factors with weight and time of death of the baby.

TABLE IV. TOTAL INFANT MORTALITY (TIME AND CAUSES OF DEATH)

WEIGHT GM.	TIME OF DEATH				CONTRIBUTING MATERNAL CAUSES					
	ANTEPARTUM	INTRAPARTUM	NEONATAL	TOTAL	TOXEMIA	ABLATIO PLACENTAE	PLACENTA PREVIA	SYPHILIS	DIABETES	INTRAPARTUM SEPSIS
Under 1,000	54	6	80	140	11	1	5	7	1	0
1,000-1,500	55	6	84	145	14	2	4	19	0	1
1,500-2,500	78	42	60	180	39	14	14	20	0	6
2,500 - -	104	104	125	333	31	20	21	17	1	14
Total	291	158	349	798	95	37	44	63	2	21

Miscellaneous Causes

WEIGHT GM.	PRE- MATURITY	PROLAPSED CORD	LIVER HEM- ORRHAGE	CONGENITAL ANOMALIES	UNKNOWN
Under 1,000	78	2	0	4	22
1,000-1,500	83	1	1	8	18
1,500-2,500	60	5	2	13	24
2,500 - -	0	11	3	23	50
Total	221	19	6	48	114

There were 95 deaths in which maternal toxemia (eclampsia, pre-eclampsia, and nephritic toxemia) was either the sole or a very important contributing factor to the death of the infant. Twenty-five of these infants were previable or weighed under 1,500 gm., and 18 of these were dead on admission. Of this latter group of 18 infants dead on admission, 9 were delivered following the spontaneous onset of labor, 3 were delivered following a medical induction, 3 following bag inductions, and 3 by means of cesarean section. Of the remaining 7 intrapartum and neonatal deaths, 2 were delivered by cesarean section, 2 delivered after spontaneous onset of labor, 2 delivered after medical inductions, and 1 delivered after a bag induction.

Seventy infants in the toxemia group weighed over 1,500 gm., and of these, 37 were dead upon admission, 11 died during labor, and 22 died during the first two weeks of life.

In the 22 neonatal deaths, autopsies were performed upon 15 infants, revealing 9 deaths due to intracranial hemorrhage. In the total series of 95 cases of infant

1,000 and 1,500 gm., the indications in this group being impending eclampsia, 3 cases; and tuberculosis for purpose of sterilization, 1 case. Ten infants weighed over 1,500 gm. but less than 2,500 gm. The indications for abdominal delivery in these cases follow: placenta previa, 4 cases; impending eclampsia, 5 cases; and previous cesarean section, 1 case. The remaining 12 infants weighed over 2,500 gm. and were delivered by cesarean section because of disproportion in 4 cases, toxemia in 1 case, placenta previa centralis in 1 case, abruptio placentae in 4 cases, previous cesarean section in 2 cases, and tuberculosis for purpose of sterilization in 1 case. Three infants in this latter group died of congenital anomalies, 1 death was due to syphilis, 4 infants died in the neonatal period from intracranial hemorrhage, two infants died of bronchopneumonia during the second week of life and one died of massive liver hemorrhage. To recapitulate, it will be noted that among the 29 infants alive on admission to the hospital, 7 were previable (under 1,500 gm.), 10 were

TABLE II. GROSS AND CORRECTED INFANT OPERATIVE MORTALITY

OPERATIVE PROCEDURE	NO.	INFANT DEATHS	GROSS INFANT MORTALITY	CORRECTED DEATHS	CORRECTED INFANT MORTALITY
Low forceps	605	31	5.1%	29	4.78%
Midforceps	96	14	14.5%	13	13.5 %
Cesarean section	288	44	15.2%	24	8.3 %
Breech extraction	30	6	20.0%	5	16.5 %
Version and extraction	108	25	23.1%	12	11.6 %
Dührssen's incision	17	3	17.6%	3	17.6 %
Braxton-Hicks version	25	25	100.0%	9	36.0 %

TABLE III. CESAREAN SECTION INFANT MORTALITY

INDICATION	TIMES PERFORMED	GROSS INFANT MORTALITY	CORRECTED INFANT MORTALITY	CORRECTED INFANT MORTALITY RATE
Disproportion	86	4	2	2.3%
Ablatio placentae	24	16	6	25.0%
Placenta previa	41	7	5	12.2%
Toxemia	62	10	5	8.0%
Previous cesarean sections	28	2	2	7.1%
Ruptured uterus	7	3	3	42.4%
Nonobstetric indications	40	2	1	2.1%
Total	288	44	24	8.3%

premature (under 2,500 gm.) and of the 12 remaining mature infants, the operative procedure selected played no part in the death of the infant. As would be expected, the largest number of previable and premature infants delivered by cesarean section occurred in the toxemic group. The lowest mortality (Table III) occurred in those cases where disproportion was the indication for cesarean section. Two of these infants died as a result of congenital anomalies, one hydrocephalus, 1 congenital atresia of the esophagus, 1 infant could not be resuscitated, and 1 infant died on the eighth day of birth of bronchopneumonia.

The Dührssen incision operation was performed 17 times. In 8 instances the presenting part was at the midplane of the pelvis, while in the remainder, the station was at a lower level. Three of these babies died, 2 following difficult mid-forceps operations and the third was delivered by craniotomy following failed forceps.

Transverse presentations were encountered 23 times, an incidence of 0.14 per cent. Fifteen were delivered by version and extraction, 6 of these following bag insertions. Seven of these babies died. Two live babies were delivered by cesarean

In the entire series, the mothers of 18 babies that were lost had been referred to the hospital after attempts had been made in the home to effect delivery. Of these, 5 might have been saved by abdominal delivery had not previous procedures made cesarean section too hazardous a procedure for the mother. Nine babies in this group died before delivery or shortly after delivery.

PROLONGED LABOR

There were 26 infant deaths occurring in cases of prolonged labor varying in duration between thirty-eight and one hundred and three hours. In 14 of these cases, the dystocia was definitely functional without evidence of disproportion. That the labors would be prolonged and difficult was recognizable after the first sixteen to twenty hours of labor. The so-called conservative attitude in the management of these cases seemed justified in view of the fact that the dystocia could be attributed solely to inefficient uterine contractions. Since accoucheurs have frequently observed these malfunctioning uteri suddenly adjust themselves after hours of irregular, inefficient contractions and result in a quick and happy termination of labor, we feel that management, conservative versus radical, must be dependent upon the judgment of the individual attendant. Of the 14 cases of inertia, 5 patients delivered spontaneously, 5 by the low forceps operation, 1 by a mid-forceps operation, 1 by a version and extraction, 1 by breech extraction, and 1 breech was allowed to deliver spontaneously. Had a timely cesarean section been performed in these cases, the results for the baby would have been different.

There were 12 infant deaths occurring in cases of prolonged labor in which disproportion of varying degrees was associated with the dystocia. In 5 cases, the disproportion was not recognized early enough in labor to justify safe abdominal delivery. Three of these patients were delivered by craniotomy after the baby had succumbed, 1 was delivered by a midforceps operation, and the fifth patient delivered spontaneously, the fetal head being markedly molded. In these 5 cases, had the disproportion been recognized, the "modus operandi" certainly would have been obvious. The remaining 7 infant deaths associated with prolonged labors fall in that ever disturbing group of cases of borderline disproportion with uterine dysfunction, and timely cesarean section could have been performed without undue criticism. Of these cases, 2 patients delivered spontaneously, 2 by low forceps, and 2 by the midforceps operation. The "impression method" is used as a routine in the Cook County Hospital to diagnose cephalopelvic disproportion. The failure of the method in these 12 cases was in a great part due to the fact that the amount of molding of the fetal head was not properly evaluated.

In reviewing these cases of prolonged labor, we find that in 26 cases error was made either in failing to recognize the cause of the dystocia or, if recognized early enough, in failing to institute the proper method of delivery.

DISCUSSION

Conflict has been noted in the literature as to the method of reporting infant mortality. It is generally accepted that only infants weighing less than 1,500 gm. and measuring less than 35 cm., head to heel, should be excluded from the corrected infant mortality (Stander¹). On this basis alone the infant mortality at the Cook County Hospital during the period included in this survey would be 513 infant deaths or 3.15 per cent. However, in compiling a corrected infant mortality rate exclusion of only infants below the above weight and length specifications would not present the true picture if a corrected infant mortality rate is to represent the result of obstetric procedure. Deaths which occur in utero before the patients present themselves to the hospital should be excluded from a corrected infant mortality, for regardless of the obstetric procedure, the outcome for the infant is obvious. Similarly,

deaths, 59 were excluded, leaving 36 deaths as a corrected infant mortality. Of these, 7 infants might have been saved had the choice of delivery been the abdominal route rather than through the natural passages. Nine infants in this group died before the onset of labor while under observation in the ward. These unfortunate deaths occurred following an attempt to prolong the pregnancy before inducing labor, so as to increase the infants' chances for survival. This experience is worthy of consideration in managing cases of toxemia where with the questionable viability of the baby the induction of labor is delayed.

During the period reviewed, ablatio placentae occurred 63 times with 37 infant deaths, a gross mortality rate of 58 per cent (Table IV). Among these, 3 were nonviable and 34 were viable, but of this latter group 22 were dead on admission to the hospital. The corrected infant mortality was 12 deaths or 20 per cent. Twenty-six babies survived this accident, 8 being delivered by cesarean section, 7 by the low forceps operation, 1 by version and extraction following bag insertion, and 9 delivered spontaneously, 1 after bag insertion. In the 7 patients delivered by the forceps operation, evidence of fetal distress with conditions favorable for immediate delivery indicated the operation. The possibility of honest error in making the diagnosis of premature separation of the normally implanted placenta may, at least in part, account for the comparatively low infant mortality. The method of delivery among the 37 infants that failed to survive this accident follows: Spontaneous delivery, 16; classical cesarean section, 2; low cervical cesarean section, 3; Porro cesarean section, 11; low forceps, 3; version and extraction after bag insertion, 3; and spontaneous delivery after bag insertion, 1.

The deaths of 2 of the 12 viable infants were predictable and, had cesarean section been selected for delivery, the lives of these infants might have been saved.

During the four-year period reviewed, there were 127 cases of placenta previa with 44 infant deaths, a gross mortality rate of 34.6 per cent. Twenty-six of these infants were alive and viable upon admission to the hospital, leaving a corrected placenta previa infant mortality rate of 20 per cent. Table V represents the methods of delivery in all cases of placenta previa.

TABLE V. PLACENTA PREVIA MANAGEMENT AND FETAL RESULTS

MANAGEMENT	TOTAL	LIVE BABIES	VIALE INFANTS DIED	NONVIALE INFANTS DIED
Abdominal section	41	34	5	2
Spontaneous delivery after bag induction	22	10	10	2
Version and extraction after bag induction	2	2	0	0
Rupture of bag of waters	22	22	0	0
No therapy required	15	15	0	0
Braxton Hicks version	21	0	7	14
Braxton Hicks after bag in- duction	4	0	4	0
Total	127	83	26	18

The 5 viable infants which died and were delivered by cesarean section succumbed during the neonatal period. Two died of bronchopneumonia, 2 of intracranial hemorrhage, and in 1 case the cause of death was undetermined. In 9 cases in which viable infants were lost, conditions were favorable for cesarean section and if performed might have salvaged some of these babies. In the remainder of these cases where viable babies were lost, the patients were bleeding profusely and were in such poor condition upon admission that cesarean section was contra-indicated.

There were 21 infant deaths due to sepsis, the fetus succumbing either in the course of the maternal sepsis, or the sepsis resulted in a premature labor, the infants dying shortly after birth. In 14 of these, lobar pneumonia was the cause of the maternal sepsis; in 5, severe pyelitis; in 1, ascending cholangitis; and in 1 other case, bacterial endocarditis.

these deaths are due to prematurity when occurring in the neonatal period. Others occur in cases where a dead infant may be expected as in ablatio placentae and placenta previa centralis, where the operation is performed in the interest of the mother. It is in cases of dystocia, such as the 26 cases in this series, where the infant has reached maturity that the more frequent performance of early cesarean section would undoubtedly diminish the infant mortality, without unduly increasing the incidence of cesarean section.

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700 NORTH MICHIGAN AVENUE

185 NORTH WABASH AVENUE

DISCUSSION

DR. FRED L. ADAIR.—It is difficult to discuss in a brief time a paper which contains such a mass of statistics. Statistics are, of course, definitely helpful in evaluating various procedures and in making comparisons. It seems important, therefore, in connection with any study of statistics to reach some more or less arbitrary standard which can be used not by one but by many. Hillis and Benenson have pointed out the lack of uniform standards for such a comparative statistical analysis.

At the Chicago Lying-in Hospital we consider as abortions all cases of less than twenty-two weeks' gestation, which is approximately five months. The law says that all cases over five months must be reported as births. The length of the fetus, 28 cm., and the weight, 400 gm., are also used as standard. One encounters certain difficulties in applying these three criteria, but if the fetus complies with any two of them, it should be placed in the abortion group. For example, if a fetus is born which is less than 28 cm. in length and less than 400 gm. in weight, but beyond twenty-two weeks, it would still be in the abortion group. Or, if the gestation period was twenty-two weeks or less and the fetus longer than 28 cm., we would still consider it an abortion.

The next group to consider is the previable group, stopping at 1,000 gm. as the maximum weight, 400 gm. the minimum; length, 28 to 35 cm.; and period of gestation, from twenty-two to twenty-eight weeks. One thousand grams have been placed as the upper margin of previability, because we find that relatively few infants survive who are under 1,000 gm. in weight. In a study of six hospitals, Dr. Dunham found that 5 of the 6 showed no survivals under 1,000 gm. One institution had 5 per cent survivals. We have had about 1.2 per cent survivals at the Lying-in Hospital, but only a very few of these babies do survive, so the term previability seems applicable to the group under 1,000 gm.

The term premature-viable is applied to fetuses weighing under 2,500 gm. and over 1,000 gm., with a length of 35 to 47 cm., and a gestation age from twenty-eight to thirty-seven weeks.

The mature fetus weighs from 2,500 to 5,000 gm., is from 47 to 54 cm. in length, and from 38 to 43 calendar weeks' gestation.

Then we have a group of excessive size fetuses which presents a problem. They can be called postmature or oversized and the following criteria for classifying them have been set: more than 4,500 gm. in weight; over 54 cm. in length; and more than forty-three weeks' gestation age.

should neonatal deaths due to congenital anomalies or syphilis be included? It is our opinion that the inclusion of these deaths in a corrected infant mortality is not a true picture of obstetric procedure, and therefore should not be included in a corrected infant mortality. The corrected mortality rate after deducting the deaths of infants under 1,500 gm. and under 35 cm., those dead on admission to the obstetric service, and those deaths due to congenital anomalies and syphilis is 289 or 1.78 per cent for the Cook County Hospital in Chicago.

A study of all cases of prolonged labor is impossible because of inadequate record facilities. As to the question of the more frequent performance of cesarean section, the outcome for the infant might possibly have been different had the operations been performed 9 times for placenta previa, 11 times for uterine dysfunction without disproportion, 11 times for borderline disproportion with uterine dysfunction, and in 7 cases for toxemia. Strangely enough the incidence of cesarean section in our series was 288 or 1.78 per cent. Had cesarean section been performed in 26 cases where the results might have been foreseen, the incidence of cesarean section would then have been 1.93 per cent. Some hospitals have reported cesarean section incidence as high as 14 per cent.

Stander² in quoting Plass, states that about 25,000 cesarean sections are done each year in this country and that probably 75 per cent of these are unnecessary. In the Woman's Clinic of New York City² in a year's period, among 5,456 deliveries, there were 153 cesarean sections, an incidence of 2.8 per cent, with 11 infant deaths. In a ten-year study at the Boston City Hospital,³ among 22,880 deliveries, there were 703 abdominal sections, an incidence of 3.07 per cent. The infant cesarean section mortality was not given. In the Touro Infirmary Obstetric Service⁴ in 1935, in 752 deliveries, 493 of which were private and 259 charity cases, there were 52 cesarean sections, an incidence of 6.5 per cent. In the Margaret Hague Maternity Hospital⁵ in Jersey City, in 8,852 cases, there were 117 cesarean sections, an incidence of 2 per cent with 21 fetal deaths or 11.8 per cent. The corrected cesarean infant mortality in this group was 5.6 per cent. Kushner⁶ reports a cesarean section incidence of 3.4 per cent at the Bronx Hospital in 3,060 deliveries. It is interesting to note that in this same institution which accepts both private and charity patients, the incidence among the ward patients was only 1.9 per cent. There were 11 infant deaths, a mortality of 11 per cent. At the Chicago Lying-in Hospital, E. F. Daily⁷ reports an incidence of 2.86 per cent in a total series including 8,871 hospital patients and 8,622 deliveries in the home service. The incidence among 8,871 hospital cases was 5.6 per cent. In this entire series there were 31 infant deaths, a gross mortality of 5.2 per cent.

J. R. McCord⁸ reports that at the Grady Memorial Hospital, in 1,721 deliveries among colored patients, there were only three cesarean sections, an incidence of 0.18 per cent, the lowest incidence we were able to find. It is especially commendable that the gross infant mortality in this series was 1.8 per cent, the corrected 1.2 per cent.

At the Rotunda Hospital⁹ from November, 1934, to October, 1935, in 2,777 deliveries there were 29 cesarean sections, an incidence of 1.05 per cent and at the Coombes Lying-in Hospital¹⁰ in 1,188 deliveries there were 37 cesarean sections, an incidence of 3.1 per cent with six stillbirths and neonatal deaths, an infant cesarean section mortality of 16.2 per cent.

It is interesting to note that in a three-year period in the entire state of Iowa¹¹ among 91,738 births, the cesarean section incidence was 1.0 per cent.

Reviewing these statistics, it is found that the general infant mortality rate in cesarean section varies from 2 per cent to 16 per cent. Most of

In the past nine years there were 7,461 deliveries. The infants numbered 7,536. The gross fetal mortality was 3.77 per cent. Subtracting the number of infants which were premature, which were born with some anomaly incompatible with continued life or which were dead when labor began as evidenced by absent heart tones, we have a corrected mortality of 1.15 per cent.

Our figures vary materially from those given by Hillis in some particulars. The number of spontaneous deliveries is far less and the incidence of operative delivery is much higher. An analysis of our work, however, indicates that the great majority of our operative deliveries are low forceps. In the entire series of cases there were only three high forceps deliveries and but 217 midforceps. Our outlet forceps are greatly increased in number by the frequent use of analgesic agents. As most of the work is done by trained men we have not tried to limit the number of outlet forceps deliveries. A study of infant mortality and its relation to various procedures made two years ago showed that infant loss of life in spontaneous delivery and that with outlet forceps were nearly identical, the mortality with outlet forceps being 0.1 per cent less than when the infants were allowed to deliver spontaneously. Outlet forceps in trained hands is not a radical procedure. A clear indication must exist for the use of midforceps and high forceps should be an exceedingly rare operation.

In the County Hospital series version and extraction occurred 108 times in 16,242. In our series 123 versions were done in 7,461 labors, the incidence being 1.63 per cent. The Cook County series lists 634 breech deliveries. I agree with the recommendation that a labor with a breech position should be allowed to proceed normally until the breech is delivered, interference beginning only after this. The wisdom of this is shown in the figures quoted, the mortality in those cases managed conservatively being far less than when extraction was needed.

Recently Galloway, in our service, collected figures upon a series of 285 breech cases occurring in 8,531 labors. Of these patients 188 were delivered at term, the mortality in this group being 5.85 per cent. A very marked difference was found between the mortality rate in the group at term and the premature infants. The greatest mortality was in the group under seven months gestation, in which the mortality was 96 per cent. In the group of infants weighing five pounds or more the mortality was 6.5 per cent.

DR. HILLIS (closing).—The inclusion in the mortality lists of babies weighing between 1,000 and 1,500 gm. raises the death rate considerably. From a mechanical standpoint a baby that weighs less than $3\frac{1}{4}$ pounds is not a very important item in the delivery. Such babies usually deliver spontaneously, forceps are not used and the version, with conditions present, is a simple thing. The death of such babies is entirely beyond the control of the attendant.

The value of prenatal care at Cook County Hospital agrees with all other large series and indicates that the death rate in the babies is much lower when the patient has been under observation during her pregnancy. Most of the benefits come from the early recognition of syphilis and the toxemias of pregnancy. We believe, at the Cook County Hospital, that impression of the head is a valuable aid in the diagnosis of disproportion between the head and the pelvis.

With respect to the forceps operation, this series indicates that 4.3 cases in every 100 require some kind of forceps delivery. The mortality in these indicated forceps operations was 4.8 per cent. To these deaths should be added 23 cases in which the baby died where low forceps should have been done in the second stage.

The infant mortality in breech labor is generally said to be 8 to 15 per cent. It is well known that unnecessary interference in a breech labor contributes largely to infant death. It requires considerable poise to allow a breech case to deliver spontaneously as far as the navel, especially if one does not constantly know that the baby is in good condition. At the Cook County Hospital the head stethoscope is worn in every labor during the second stage and the breech cases are allowed to deliver spontaneously as far as the navel. Manual aid is done only when necessary and breech extraction is never done except for a definite reason.

The following terms have also been adopted: antenatal death, when death occurs before the onset of labor; intranatal death, when death occurs during labor; postnatal death, when the fetus shows signs of life at birth but in whom no respiration is established; and then the final or neonatal group in which the baby is born alive but dies before leaving the hospital, usually within a two weeks' period.

That represents our grouping. There is insufficient time to discuss all the factors that have been brought out by Hillis and Benensohn in their very complete presentation. It seems that, in correcting statistics, one has to distinguish between the mortality which is attributed to the institution and the mortality which is assigned to some procedure or condition associated with the death. The statistics on institutional mortality must remain as institutional mortality; they really cannot be corrected. Deaths that occur in the institution are chargeable to the institution, although not necessarily in the sense that the institution is responsible. When, however, one attempts to evaluate a given procedure from a scientific point of view, then an attempt should be made to evaluate that procedure as far as the results are concerned in mortality and morbidity. Naturally one cannot assign the death of a fetus to an operation when the fetus was already dead before the operation was begun. Certain corrections then would be justifiable in evaluating statistics of causes of death whereas one would not be justified in correcting total institutional figures.

I want to say a few words about cesarean section. It is done for the benefit of both the mother and the fetus. Ordinarily it is considered a safe procedure as far as the baby is concerned. I think these statistics emphasize the fact that there is a definite fetal mortality associated with cesarean section, and our findings at the Chicago Lying-in Hospital furnish confirmation of this thought. From May 1, 1931, to October, 1936, we had 838 sections, which was 5.8 per cent of our total deliveries for that period. There were 49 infant and fetal deaths, a total mortality of 5.8 per cent. The stillbirth rate was 1.2 per cent; the neonatal mortality rate, 4.6 per cent. If we consider the uncorrected mortality for all the cases in the hospital, the neonatal mortality was 1.83 per cent compared with the 4.6 per cent associated with cesarean section. Our stillbirths were somewhat higher in the non-cesarean than in the cesarean group. In other words, we did not do cesarean section when the baby was already dead or in a precarious condition.

It was interesting to study why a larger percentage of cesarean babies should die neonatally—why the neonatal mortality in our cesarean section group was 4.6 per cent, whereas the uncorrected neonatal mortality for all cases in the hospital was less than 2 per cent. Of the 49 fetal deaths (4.6 per cent), 31 were neonatal and 18 were stillbirths. The neonatal were associated with abruptio placentae in 8, placenta previa in 2, malformation in 4, eclampsia in one, and with premature birth and undetermined cause in 16. Of these 31 neonatal deaths, 19 infants weighed less than 2,500 gm. Of the 18 stillbirths, 15 were associated with abruptio placentae, 2 with placenta previa, and one with eclampsia.

In a subsequent series of 338 sections we have had 18 infant and fetal deaths—14 were neonatal and 4 were stillbirths. Of these 18 deaths, 4 (of which 3 were stillbirths) were associated with placenta previa, 4 with abruptio placentae, 3 with heart disease, 3 with previous section, one with transverse presentation, one with prolonged labor without progress, one with epilepsy, and one with Porro section.

One must recognize that about one out of 20 babies is lost when cesarean section is done. It behooves us therefore to select cases very carefully when there is not a strict maternal indication for this operation. Every effort should be made to secure 100 per cent fetal survival in association with cesarean section.

DR. WILLIAM C. DANFORTH.—I would like to offer for comparison with the report of Dr. Hillis some figures from our service which differs from that of the County Hospital in that a considerable percentage of our patients are private cases. Eighty per cent of the work in the maternity is done by the departmental staff, all of whom also belong to the Department of Obstetrics and Gynecology of Northwestern University Medical School. There is also a selected group of practitioners. Uniformity of technic is therefore not difficult to maintain.

Thus, in gonadectomized, immature rabbits the oxygen consumption increases 20 per cent in five hours (after a single subcutaneous injection of 500 international units of estradiol); by the tenth hour, it increases 37 per cent and by the twenty-fourth hour, the rate of oxygen consumption is 60 per cent greater than before the administration of estrin (see Fig. 1, Curve B). Thus the effect is approximately two-thirds complete by the tenth hour after the injection of estrin.²⁰

This fact is significant when it is recalled that under the most favorable circumstances of estrin administration the myometrium shows no appreciable motility for about ten hours,^{5, 25-27, 29} and from this time on, until the twenty-fourth hour or thereabout, the activity of the myometrium increases progressively to maximal forcefulness and rhythmicity (see Fig. 1, Curve C). Pertinent also is the observation that addition of estrin to a bath containing inactive uterine tissue fails to render the myometrium active; in order for excised tissue

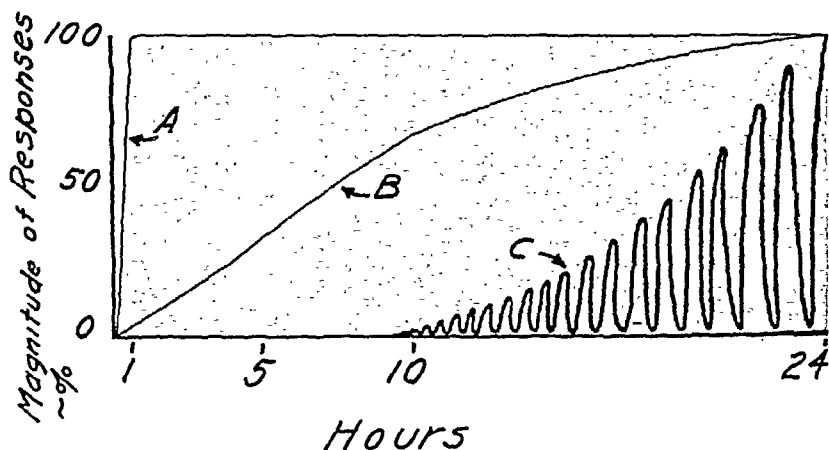


Fig. 1.—Diagram showing the relation of certain effects of estrin upon the uterus after administration to a rabbit. A, initial hyperemia of small vessels in the uterus (endometrial and myometrial); B, oxygen consumption of uterine tissue; C, the development of uterine contractions in vivo. Ordinate, the magnitude of the several responses in terms of percentage of the maximal response; abscissa, time in hours after a single subcutaneous injection of estradiol or other estrogenic hormone.

to exhibit estrous motility the hormone must have acted first in vivo.^{5, 15, 22, 24, 28, 29} Clearly, therefore, the onset of the estrous type of motility is preceded by an appreciable elevation of metabolic activity of the uterus which has been achieved only in vivo up to the present time. Hence the onset of this type of motility signifies that a certain phase of the uterine growth response to estrin has been attained. That myometrial activity is not essential for endometrial growth is shown by the fact that transplants of endometrium grow in the anterior chamber of the eye in the absence of myometrial tissue.^{21, 23} For the organ as a whole, however, and for the myometrium alone, perhaps, the intermittent contractions of estrus do play an important role which has been appreciated only in the past few years.

THE ACTIVATION OF UTERINE MUSCLE BY ESTRIN AND ITS RELATION TO UTERINE GROWTH

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DURING proestrus and estrus, the myometrium exhibits a characteristic pattern of motility. Each intermittent contraction of the uterus normally arises as a continuation of a tubal contraction, every fourth or fifth one of which finds the uterus relaxed and ready to contract again.^{25, 31} This wave of myometrial contraction sweeps slowly over the length of the uterus and subsides as it reaches the cervix. Not only does the whole intact uterus show this dominance of the upper portion over the lower one but parts of the uterus, excised as well as in situ, show a similar gradient of activity independently of the tubes.^{4, 7, 8, 16, 17, 21, 32 et al.} The effect is perhaps most strikingly shown when the contraction frequencies of the upper and lower ends of a uterine horn are investigated separately, for it is found that the tubal segment has a higher frequency of contraction than does the cervical end studied under similar conditions.^{4, 12, 14}

Such a gradient of activity is dependent upon the hormone, estrin, which is the hormone responsible for the other manifestations of estrus.²⁶⁻²⁸ Careful consideration of the data at hand shows that the manner in which estrin exerts its effect upon the myometrium is ascribable to the action which this hormone has upon the cells of this tissue and not to any known effect which it may have upon the innervation, extrinsic or intrinsic.^{16, 27} The action is, therefore, essentially a metabolic one.

Ample evidence exists which shows that the uterus has a higher rate of oxygen consumption at the time of estrus than it does at any other time in the nongravid state,^{3, 10, 18-20} and this, like myometrial activity, has been shown to be due to the action of estrin.^{3, 10, 18, 20} Up to the present time, however, no evidence has been adduced which shows whether the increased oxygen utilization of the uterus is attributable to the marked activity which the myometrium undergoes at this time, as suggested by King,¹⁹ or whether the uterus is active because there is an initial increase in the rate of oxygen consumption prior to the onset of motility. Experiments bearing upon this point have recently been performed.

THE METABOLIC STIMULUS IN RELATION TO ONSET OF MOTILITY

When estrin is injected into suitable ovariectomized animals, a rise in the rate of oxygen consumption takes place within a few hours.

*Fellow, John Simon Guggenheim Memorial Foundation. The writer expresses his appreciation to Professor George W. Corner for advice and hospitality extended to him during tenure of the fellowship.

going marked growth changes coincidently. Because of the fact that the uterine motility of estrus is in reality part of the uterine growth response, as noted above, one may thus say that uterine growth is its own best means of providing an ample blood supply for itself. Nature has made sure, therefore, that that hormonal agent which is the primary metabolic stimulus to the uterus anticipates this action by supplying blood through the agency of a local vasodilatation and subsequently provides an adequate mechanism for the facilitation of the circulation of blood through, and of lymph from, the growing organ at a time when the nutritive requirements are increased. That this mechanism is a beneficial one is shown as a result of experiments on animals.

AUGMENTATION OF UTERINE GROWTH BY AUGMENTATION OF THE BLOOD SUPPLY

The experiments which show the importance of the local blood supply for uterine growth are not new. They were performed a number of years ago by Buchheim and Zaleski⁶ who studied its relation to endometrial growth, and by Courier and Bouin⁹ who studied its relation to myometrial growth. The methods and results were similar, only the tissues were different. In one set of experiments⁶ a transplant of endometrial tissue was made to each ear of a rabbit, in the other,⁹ myometrial transplants were made. After the transplants became established, the cervical sympathetic nerve to one ear in each rabbit was sectioned. The composition of the blood flowing to each ear was, of course, identical although the volume flow of blood was much increased in one ear and not in the other. It was found, as a result of these procedures, that the amount of growth on the side with the increased blood supply was far greater than it was on the opposite, control side. Indeed, Buchheim and Zaleski state that the amount of growth observed by them was almost pathologic.

* * * * *

While it is evident, therefore, that the effect of estrin on uterine tissues is chiefly that of a growth-promoting agent, the other uterine effects brought about by the same hormone play a subsidiary but important role which assures that the main effect will take place in due time. The initial vasodilatation of the small vessels provides an immediate and easy access of blood to the inactive uterine tissues whose metabolic processes are at low ebb. As the hormone raises the metabolic activity of the uterus to a certain level the myometrium becomes rhythmically active, and this motility in turn aids the growth changes which proceed simultaneously through the agency of the improved state of the local circulatory conditions. Thus these several effects which are brought about in the uterus by the administration of estrin are so inter-related that uterine growth is achieved, from the physiologic point of view, in a most efficient manner.

THE ROLE OF INTERMITTENT UTERINE CONTRACTIONS DURING ESTRUS

Prominent among the effects which estrin has upon the uterus is the vascular change which comes about within a few minutes after the injection of the hormone. Within twenty minutes to half an hour, a state of maximal hyperemia exists^{21, 23, 25} which persists as one of the most striking of the phenomena associated with the response of the uterus to estrin (see Fig. 1, Curve A). As a result of this hyperemia enlargement of the capillary bed, increase in the permeability of the vessels, particularly in the endometrium, and accumulation of appreciable quantities of fluid in the stroma of this structure take place.¹³ These effects are well developed before the myometrium is motile and, according to the evidence at hand, they precede any significant rise in the metabolic activity of the uterus.²⁰ This consideration suggests that the increase in vascularity which takes place first is the result of a special, direct mechanism whose chief function is to assure an adequate circulation to an ischemic organ whose blood vessels are small, which has a low level of metabolic activity and which is non-motile. Enlargement of the vascular bed by a local vasodilatation thus provides the tissue with an ample supply of blood. That a vasodilating substance is elaborated locally is shown by the fact that the initial hyperemia takes place in transplanted uterine tissues in which nerves have not been demonstrated,^{21, 23} and since the hyperemia can be temporarily inhibited by the injection of atropine.²⁵ As yet, however, existence of this vasodilating substance has not been directly proved, although the initial vasodilatation has.*

Thus far the relation of uterine activity to the preliminary vascular and metabolic changes has been only a subject of theoretical discussion^{13, 27} and not one of direct investigation. The conclusion has been reached, on the basis of sound physiologic considerations, that the intermittent uterine contractions serve to augment the volume flow of blood through the already dilated vessels of the uterus, owing to the pumping action of the myometrial movements. Such, at least, is the effect of intermittent activity in skeletal muscle and of rhythmic intestinal movements.² Activity of this type has been found to be essential, moreover, for the formation and flow of lymph from a number of structures.¹¹ It is for this reason, no doubt, that only at the time of estrus can the lymphatic vessels of the female genital tract be injected with ease.¹ By inference, therefore, it appears that the plasma fluid which contributes to the edema of the endometrium after administration of estrin tends to be removed by the intermittent uterine contractions of estrus;^{13, 27} failure of such an action would predispose to retention of large quantities of fluid in this tissue. It is clear from these considerations, then, that the uterine contractions which are induced by estrin serve the purpose in the intact animal of assuring an adequate circulation through tissues which are under-

*Experiments done since this was written established that this substance exists and is identical in its reactions with acetyl-choline. An account of these experiments will be published elsewhere.

24 patients who underwent surgical treatment but failed to reply to the questionnaire. The total number of patients in whom medical treatment was employed, therefore, should have read 405 and the total number of patients in whom surgical treatment was employed should have read 128. The results of these operations will be the subject of this report. Follow-up letters were sent to all the patients who underwent operation. Thirty-four patients were not heard from; this leaves 94 cases in which the state of health of the patient is known one or more years after operation.

It is somewhat difficult to evaluate the efficacy of any one operation in the relief of dysmenorrhea as one or more surgical procedures frequently were done at the one operation, depending on the pathologic condition which was present. Therefore, the cases have been grouped according to the most important surgical procedure performed.

Resection of the presacral nerve has been the subject of much interest in the surgical control of dysmenorrhea. The pain was considered severe enough to warrant the performance of this operation in 15 cases (Table I). In 7 cases other surgical measures were carried out at the

TABLE I. RESULTS OF OPERATIVE TREATMENT IN CASES OF DYSMENORRHEA

TYPE OF OPERATION		TOTAL NUMBER	RELIEF		
			COMPLETE	PARTIAL	NONE
Resection of pre-sacral nerve	Alone	8	2	3	3
	With resection of endometrial implants	3	2	1	0
Uterine suspension	With uterine suspension	3	1	1	1
	With myomectomy	1	1	0	0
	With resection of ovaries	5	2	2	1
	With removal of endometrial implants	1	0	1	0
Dilatation and curettage	With dilatation and curettage	3	0	2	1
	With myomectomy	3	2	0	1
	Alone	26	5	12	9
	With removal of cervical fibroid	1	1	0	0
	With partial resection of ovaries	2	0	2	0
Partial resection of ovaries	With myomectomy	1	0	0	1
		2	0	1	1
Myomectomy		3	1	1	1
Insertion of a Baldwin tube		4	0	2	2
Miscellaneous	Watkins-Wertheim interposition	1	1	0	0
	Salpingectomy	1	0	1	0
	Exploratory laparotomy and freeing of adhesions	1	0	0	1
Hysterectomy	Total, combined with removal of ovaries	14	6	8	0
	Total, without removal of ovaries	7	2	5	0
	Subtotal, combined with removal of ovaries	4	3	1	0
Total		94	29	43	22

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SURGICAL TREATMENT OF DYSMENORRHEA*

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THE many types of treatment, both medical and surgical, which have been proposed for the cure of dysmenorrhea are so numerous that it is evident that no type of treatment is entirely satisfactory. In an attempt to evaluate the results of treatment of dysmenorrhea, the histories of 682 cases were reviewed. These cases included all those in which a diagnosis of dysmenorrhea was made at the Mayo Clinic between Jan. 1, 1931 and Jan. 1, 1934. In 112 cases the dysmenorrhea was not considered of sufficient severity to require medication. In 405 cases medical management alone was instituted. These cases have been the subject of a previous report by Stacy and Shoemaker. Surgical treatment was advised but refused by the patient in 37 cases and 128 patients underwent operations. In the paper by Stacy and Shoemaker the total number of cases in which medical treatment was employed was given as 391, and the number of cases in which surgical treatment was employed was given as 104. In reviewing these figures for the present paper, it was discovered that the 38 cases which were discarded from consideration because lesions in the pelvis were thought to be responsible for the dysmenorrhea included 14 patients who received medical treatment and

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case in which it was performed for the removal of a subserous myoma, the patient did not obtain any relief. Improvement occurred in both of the cases in which partial resection of the ovaries was combined with dilatation and curettage.

Partial resection of the ovaries was the only surgical procedure employed in 2 cases. Improvement occurred in one of these cases, but no improvement was noted in the other case.

Myomectomy was performed alone in 3 cases. Complete relief occurred in one of these cases, partial relief occurred in another case, but no benefit was noted in the third case.

In 4 cases a Baldwin tube was inserted for a short period of time, presumably to provide dilatation of the os. This operation was popular some years ago, but as little success attended the procedure, it has been almost discarded in recent years.

In 3 cases miscellaneous operations gave varying results. Complete relief was experienced after a Watkins-Wertheim interposition operation for prolapse of the uterus. A salpingectomy produced improvement in one case, but an exploratory laparotomy and the freeing of some adhesions failed to influence the dysmenorrhea in another case.

In 37 cases the severity of the dysmenorrhea, combined with the age of the patient and the pathologic findings resulted in the performance of a hysterectomy. A few of these patients were in their early thirties but the majority of them were more than forty years of age. Twelve of the patients who were subjected to this operation did not reply to our letters, so we have definite information in only 25 cases in which this operation was employed. In 11 of these cases the patients have felt completely well since the operation and have not had pain of any kind. In 8 of these 11 cases a total abdominal hysterectomy was performed and some ovarian tissue was preserved in all but two of them. Endometriosis was also present in one of the cases. Subtotal hysterectomy was performed in only 4 cases; in one of these cases the etiology of the pain, which had occurred between the menstrual periods and had been relieved by the onset of the menstrual flow, was pelvic tuberculosis.

In 14 cases the patients reported that they still had pain. In 9 of these cases, ovarian tissue was preserved, the right ovary was preserved in 7 of these cases, both of the ovaries were preserved in 2 cases, and in 5 cases all ovarian tissue was removed. In 6 cases the pain is mild and in 2 cases it is more severe. The patients described it as a soreness or dull aching which may be situated in any part of the abdomen; it occurs only when they are tired, and it is of short duration. Only 2 patients mentioned any periodicity of the pain. One described a steady pain in the center and right side, and said that "the last part of the month is worst." A patient who was subjected to total hysterectomy wrote that she experienced pain in the right lower quadrant of the abdomen at the menstrual period and at other times if she exerted herself or did any work. In both these cases the right ovary had been partially resected to preserve some ovarian function. A tender ovary may be the cause of the

same time; namely, resection of endometriosis in 3 cases, suspension of the uterus in 3 cases, and myomectomy in one case. In 5 cases complete relief of the dysmenorrhea followed the operation, and in another case relief was complete for two months and then the patient had a recurrence of pain which was, however, controlled by the administration of acetylsalicylic acid. Four patients were definitely improved; another patient rated her improvement at 75 per cent. Four of the patients reported no relief at the time they received our letters. This does not necessarily mean that the operation itself was at fault, but points to the use of caution in the selection of patients for resection of the presacral nerve. The mental make-up of the patient must be taken into consideration as well as the physical findings. This is well illustrated by a case in which the patient, who was a young girl, is still suffering a year after her operation. Resection of the presacral nerve was requested, as a last hope, by the family against the advice of both the physician and the surgeon, who realized that the mental attitude of the patient was such that there was no hope for alleviation of the pain.

Retroversion has long been diagnosed as the cause of many symptoms among these patients. In 12 cases in this series a suspension of the uterus was done as the primary surgical procedure. Additional pathologic changes necessitated partial resection of the ovaries in 5 cases. Removal of endometrial implants, dilatation and curettage, or myomectomy was also done in some cases. Four patients reported complete relief of their monthly pain. Two of these had undergone partial resection of the ovaries and two had undergone myomectomy in addition to suspension of the uterus. Five patients obtained partial relief of their pain and only 3 reported that they did not experience any relief as a result of the operation. Two of these patients had undergone the same two types of operation as had the 4 patients who obtained complete relief. The third failure followed a dilatation and curettage in combination with the suspension.

Dilatation and curettage was long considered to be the treatment par excellence in cases of so-called obstructive dysmenorrhea. It is often the operation of choice because there is a coincident sterility, which, if relieved, may cure the menstrual pain. However, in this group of cases there were only three in which sterility also was a factor. Dilatation and curettage was the only surgical procedure employed in 26 cases; in 2 cases it was done in combination with myomectomy, and in one of these cases the myomectomy was performed by the vaginal route in the course of removal of a pedunculated submucous fibroid. In 2 cases it was done in combination with resection of the ovaries. Five patients obtained complete relief, but another patient reported that she had obtained complete relief for one year. Fourteen patients were improved for from three months to two years. Ten reported no benefit at all from the procedure. Myomectomy was performed twice in conjunction with dilatation and curettage. In the case in which it was performed in the course of removal of a pedunculated submucous fibroid protruding through the cervical os, the patient obtained complete relief, but in the

hormonal basis for dysfunctional menstrual disorders or sterility are appreciated by all gynecologists. It is then not surprising that endometrial biopsy, performed without anesthesia, has been widely adopted as an office procedure.

Various cannula-like instruments have been devised for biopsy of the endometrium (Klingler and Burch,² Lörincz,³ Novak,⁴ and Randall⁵). In our experience, these instruments are inadequate for diagnostic purposes even in dysfunctional states of the endometrium, inasmuch as one procure at best only 4 strips of tissue which may not be representative of the endometrium as a whole. That the response of different portions of the endometrium varies greatly to hormonal stimulation was shown previously (Bartelmez,⁶ Traut and Kuder,⁷ and Mazer⁸). While one may reasonably contend that the biopsy technic is sufficient in the study of selected endocrinopathies and sterility, it is certainly inadequate in the differential diagnosis between benign and malignant uterine bleeding. For these reasons, we employ diagnostic office curettage, usually without anesthesia, as suggested by Kelly,¹ in preference to the cannula-biopsy technic.

The most important indication for a diagnostic curettage is menometrorrhagia in women at or just beyond the climacterium when malignancy of the uterine fundus is frequently encountered. Many women are either unwilling or financially unable to enter a hospital for this purpose unless the imminent danger of overlooking a carcinoma is broached. Most patients insist on medical treatment for the control of uterine bleeding before consenting to hospitalization. This is the age of carcinomaphobia when one hesitates to dangle the threat of cancer before the average patient, especially, when the incidence of carcinoma in menometrorrhagia encountered in office practice, as illustrated in the present series, is only 3 per cent (5 in 163 cases, Table II). On the other hand, no physician is justified in assuming that abnormal uterine bleeding at any age is benign without recourse to definite diagnostic measures. When the possibility of carcinoma is not brought to the patient's attention, there is more than a likelihood of procrastination and loss of valuable time in detecting the true state of affairs. Illustrative of the tendency of women to neglect abnormal uterine bleeding is the fact that only 88 (52.7 per cent) of the 163 patients curetted for menometrorrhagia submitted even to an office curettage during the first three months of arrhythmic bleeding. By employing office curettage, the gynecologist avoids delay in diagnosis and spares the patient the unpleasant anticipation of hospitalization and the expense of an operating room procedure.

SELECTION OF PATIENTS AND TECHNIC

The use of the fenestrated curette as an office instrument demands the application of an aseptic technic and a modicum of both art and skill, which remove it to the realm of the gynecologist. Obviously, in selecting the patients for office curettage, certain rules of exclusion must be observed. The procedure may be readily undertaken in all married women with aberrations of the menstrual function

pain. In one case the pain in the lower part of the back had been so severe that she had taken roentgenologic treatments two to three times a year for relief. Her health is poor. In the three remaining cases in this group, the pain is situated in the right upper quadrant of the abdomen. It is difficult to evaluate the symptoms in these cases from the answers to the questionnaire and in many if not all cases it is probable that the present pain is different from the previous dysmenorrhea. In one case at least, the pain would seem to be attributable to the gall-bladder, if one can judge from the patient's description.

SUMMARY

Surgical intervention for the alleviation of dysmenorrhea produced complete relief in 29 cases and was of benefit in an additional 43 cases. In 14 cases in which hysterectomy was performed the patients still complain of some pain which can be attributed to a tender ovary in some of the cases. In 22 cases there was no relief of the dysmenorrhea. The only procedure which produced uniformly poor results was the insertion of the Baldwin tube, but this procedure has subsequently been discarded.

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THE SAFETY AND ADVANTAGES OF OFFICE CURETTAGE*

AN EVALUATION OF THE ENDOMETRIAL FINDINGS IN 305 PATIENTS

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FOURTEEN years ago, Howard A. Kelly,¹ in addressing this Society, advocated office curettage in this manner: "In doing this I suggest a technic for the specialist, which I condemn for the general practitioner lacking special skill and experience. Let it therefore be made plain that I speak only to gynecologists and of curettage for diagnostic purposes. . . I have seen no accidents following this procedure. I have made innumerable examinations of suspectedly healthy uteri, many of carcinoma of the body and intracervical, and occasionally find retained decidual products."

The value of endometrial study in gynecologic patients is now too obvious to require emphasis. Such study is not only informative concerning the presence or absence of malignancy but, inasmuch as pituitary-ovarian function is usually mirrored in the endometrium, study thereof is also helpful in an evaluation of the patient's endocrine status. In respect to the latter, endometrial study is often more useful than both blood and urine hormone determinations. The desirability of recognizing an early adenocarcinoma and the value of detecting a

*Read at a meeting of the Obstetrical Society of Philadelphia, January 6, 1938,

TABLE I. ANCILLARY DATA AND CONDITIONS INDICATING CURETTAGE IN 305 PATIENTS

Ages: 19 to 64 years
 Parity: Nulliparas 143
 Primiparas 58
 Multiparas 102

CONDITIONS	NO. PATIENTS
Menometrorrhagia	163
Sterility	109
Amenorrhea	11
Induced hyperestrinemia (postmenopausal)	10
Premenstrual tension	8
Breast hyperplasia	4

ectomy showed no trace of the lesion. Likewise, the early elimination of malignancy as a diagnostic possibility by office curettage in the premenopausal bleeding group permitted a mode of treatment other than the application of radium which is the usual procedure in hospital practice and which is so frequently followed by severe castration symptoms. Although not germane to the subject under discussion, the endometrial findings in the several groups subjected to curettage are presented because of the current interest in endometrial physiology.

ENDOMETRIUM IN MENOMETRORRHAGIA

The menometrorrhagia in 96 of the 163 patients curetted was of the dysfunctional type. The causes of the abnormal uterine bleeding in the remaining 67 were widely diversified (Table II). The endometrial findings in the 96 patients with dysfunctional uterine bleeding (Table III) confirm, in the main, the observations of others (Burch,⁹ Campbell,¹⁰ Hamblen,¹¹ Kurzrok and Wilson,¹² Rock and Bartlett,¹³ and Payne¹⁴ and others) that there is no uniform endometrial pattern in this condition. In this series of 96 cases of dysfunctional uterine bleeding, the endometrium was hyperplastic in 67.7 per cent, proliferative in 17.7 per cent, atrophic in 9.3 per cent, and secretory in 5.3 per cent. It is, thus, apparent that endometrial hyperplasia is not a necessary accompaniment of dysfunctional uterine bleeding. Computation of the exact incidence of hyperplasia in any series of dysfunctional uterine bleeding depends on the histopathologic concepts of the observers and the time relation-

TABLE II. CAUSES OF ABNORMAL BLEEDING IN 163 PATIENTS SUBJECTED TO CURETTAGE

CAUSES	NO. PATIENTS
Dysfunctional	96
Cervical erosion (5) }	28
Cervical polyps (23) }	
Fibroids	11
Estrogen-induced (postmenopausal)	9
Ovulation bleeding	6
Adenocarcinoma	5
Dysfunctional, unrelieved by intrauterine irradiation	5
Incomplete abortion	2
Senile (atrophic) vaginitis	1

or sterility, *unless* the history and preliminary pelvic examination suggest the presence of either an accident of pregnancy or pelvic inflammation. The present series, in which these criteria were rigidly applied, illustrates the relative harmlessness of office curettage. Only 2 (0.65 per cent) of the 305 patients had a temporary reaction in the form of pelvic pain and slight rise in temperature. Perforation of the uterus in 1 of the 2 patients and a mild infection in the other necessitated rest in bed for a week.

The preparation of the patient is performed as inostensibly as is possible in order to avoid the annoying emotional reaction which, in the average woman, follows the warning that a technical procedure is to be undertaken. The instruments required, previously sterilized, are kept from the patient's field of vision. She remains in the usual lithotomy position following the bimanual examination which always precedes the curettage. The vulva and vagina are cleansed with tincture of green soap and water. The portio, exposed by a bivalve speculum, is painted with 3 per cent tincture of iodine and grasped by a bullet forceps. The bivalve speculum is replaced by a weighted one. The cervical canal is then iodized and the direction and depth of the uterine cavity verified by the passage of a uterine sound. In multiparous women, the smallest (No. 1) Sims' sharp curette may then be passed without difficulty. However, in some nulliparous women, the cervical canal is narrow and requires preliminary dilatation. In such instances, the smallest metal dilator, moistened by a sterile water-soluble lubricant, is passed beyond the internal os. Following this, the curette readily enters the uterine cavity, sedulous care being observed to avoid injury to the neighborhood of the internal os. The interior of the uterus is assiduously investigated and curetted in a routine manner. At the conclusion of the procedure, the patient is permitted to rest on the table for from ten to fifteen minutes and instructed to remain at rest at home until the following morning.

The endometrial tissue, escaping easily from the cervical canal, is collected and immediately placed in 4 per cent solution of formalin for fixation. All fragments of tissue are subsequently hardened in alcohol, sectioned in paraffin, and stained by a routine hemotoxylin-eosin technic. By this procedure, a microscopic diagnosis of the endometrium is possible within seventy-two hours.

When this procedure is gently performed and when the mobilization of the cervix is preceded by a soothing word of warning, the patient experiences no pain up to the point of actual curettage. Anesthesia is generally not required but, if the patient is unusually apprehensive, a brief inhalation anesthesia may be employed at this time. Approximately 10 per cent of our patients were rapidly and safely anesthetized for momentary periods by ethyl chloride inhalation. Although this anesthetic has proved eminently satisfactory in our hands, we are, nevertheless, cognizant of its inherent dangers and recently have employed in these instances nitrous oxide and oxygen from a portable inhalation apparatus.

ANALYSIS OF 305 OFFICE CURETTEMENTS

The present report comprises a series of 305 consecutive office curettements performed during the period between Oct. 1, 1934 and Oct. 1, 1937. The youngest patient was 19 years of age and the oldest 64. Of the 305 women, 160 had borne 1 or more children and the remaining 145 were nulliparas. The chief indications for curettage in this series were menometrorrhagia and sterility. Clinical experimentation was the sole reason for curettage in a smaller group of patients (Table I).

Some very interesting data relative to current gynecologic problems were gathered which differ from those uncovered in hospital practice. For instance, 4 of the 5 adenocarcinomas were at such an early stage of development that examination of the uterus following panhyster-

Of the 109 regularly-menstruating sterile women curetted premenstrually in the course of diagnostic studies, 36 (33 per cent) showed a total absence of the secretory phase. In 18 the endometria were proliferative, in 13 hyperplastic, and in 5 hypoplastic. In the light of our present knowledge concerning the factors involved in pseudomenstruation, the latter group with hypoplastic endometria were presumably ovulating and luteinizing, but their uteri failed to respond to the ovarian stimulus.

Primary dysmenorrhea was an additional complaint in 15 of the 109 sterile women subjected to a premenstrual curettage. In view of the current interest in the probable endocrine origin of dysmenorrhea and in view of the fact that the presence of a secretory endometrium implies an intact pituitary-ovarian mechanism, the endometrial findings in this group are especially noteworthy. Only 5 (33.3 per cent) of the 15 endometria failed to show the normal secretory phase, an incidence of pseudomenstruation no greater than in the entire group of sterile women. We must, therefore, conclude, in agreement with Lackner²³ and others, that there is no definite relationship between dysmenorrhea and the endometrial pattern.

THE ENDOMETRIUM IN AMENORRHEA, PREMENSTRUAL TENSION, AND IN ABNORMAL BREAST HYPERPLASIA

Realizing the hazard of drawing conclusions from observations on small groups of patients such as these 3 conditions represent in this report, we herein merely stress certain salient features of general interest.

Eleven amenorrheic women were curetted for the purpose of determining the functional state of the endometrium in relation to the estrogen content of the blood and urine. The latter was subthreshold or acyclic in 7 women and normal in 4. The endometrium in 6 of the 11 amenorrheic women was proliferative to a degree comparable to that seen in pseudomenstruation. The patients were, nevertheless, amenorrheic, indicating the correctness of Hartman's theory²⁴ of the existence of a bleeding factor, which was apparently absent in these patients. The endometrial specimens of the remaining 5 amenorrheic patients showed hypoplasia. It is interesting to note that 1 of the 5 patients with atrophic endometrium had never menstruated (primary amenorrhea) but, nevertheless, showed a normal level of estrogenic substance in both blood and urine, pointing to the presence of a congenital defect in the Müllerian tract. The endometrium of this patient, moreover, subsequently failed to respond to more than one-half million rat units of estrogen given during a period of two months.

This phenomenon, congenital or acquired nonresponsiveness of the endometrium, was further illustrated by the endometrial atrophy found in 7 of 10 postmenopausal women (Table I) who were receiving huge doses of estrogen (10,000 rat units in oil, given intramuscularly every fourth day for a period averaging four months) for the control of severe menopausal symptoms. The remaining 3 of the group of 10 women curetted during or at the termination of treatment showed an estrogen

ship between the onset of the bleeding and the diagnostic curettage. In the absence of changes in the capillary walls or disparity in the size of the glands, it is often difficult to distinguish between a proliferative (interval) and an exaggerated proliferative (hyperplastic) endometrium. Moreover, it is of no special importance to make this distinction, inasmuch as the pathogenesis of the abnormal bleeding in both types of endometria is similar—prolonged, though not necessarily excessive, production of estrogen, unantagonized by the corpus luteum hormone, progesterin. The varying degree to which different portions of an endometrium may respond to the same hormonal stimuli is well-illustrated in the present series. No less than 16 of the 96 endometrial specimens obtained during the course of dysfunctional bleeding showed mixed patterns of hyperplasia, atrophy, and the secretory phase (Table III). The endometrial picture in dysfunctional bleeding is not appreciably influenced by the age of the patient, except in instances of atrophy which occur most frequently in postmenopausal women.

The interesting finding of a premenstrual (secretory) endometrium in 5 patients with dysfunctional uterine bleeding (Table III) supports the recent contention of Traut and Kuder⁷ that irregular shedding of the functional layers may be the immediate cause of prolonged or excessive bleeding.

ENDOMETRIUM IN FUNCTIONAL STERILITY

The complete dependence of human reproduction on the integrity of the endometrial cycle is too well-known to require elucidation. However, not until recently did gynecologists appreciate the importance of

TABLE III. ENDOMETRIAL PATTERN IN 96 PATIENTS WITH DYSFUNCTIONAL UTERINE BLEEDING

ENDOMETRIUM (Obtained during bleeding)	NUMBER	PERCENTAGE
Hyperplastic	49	51.0
Hyperplastic with patches of atrophy or premenstrual response (mixed pattern)	16	16.7
Proliferative (interval)	17	17.7
Hypoplastic (atrophy)	9	9.3
Premenstrual (secretory)	5	5.3

endometrial studies in functional sterility. Based on the studies of Heape,¹⁵ Hartman¹⁶ and Corner¹⁷ on the seasonal anovulatory bleeding of monkeys, several investigators¹⁸⁻²¹ have shown that its counterpart, pseudomenstruation, exists in the human female. This form of cyclic uterine bleeding, clinically indistinguishable from normal menstruation, occurs from an endometrium without secretory (nidation) changes. Elsewhere²² it was shown that pseudomenstruation is one of the important factors in the etiology of barren marriages. The diagnosis of this condition in regularly-menstruating sterile women rests on a study of the endometrium obtained prior to or at the very beginning of menstruation. For this reason, premenstrual curettage is a valuable part of our armamentarium in the study and treatment of sterility.

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2116 SPRUCE STREET.

21ST and SPRUCE STREETS.

DISCUSSION

DR. FLOYD KEENE.—The advantages to the patient of office curettage and its value as a means of diagnosis in both functional and organic disease are incontrovertible. Acceptance or rejection of this procedure depends upon whether it can be carried out with the same degree of safety and thoroughness as obtains with the patient under anesthesia in the hospital. In answer to this, the authors report their experience in 305 patients. Complications occurred only twice: Perforation of the uterus in one and a mild infection in the other. In 258 patients, the curettage was employed in the course of functional studies, and in 47, there was organic disease of the uterus, cervix, or vagina. Among the latter, there were 5 cases of adenocarcinoma, 4 of these lesions being so early that no cancer was found in the extirpated uteri.

In the face of such evidence, adverse criticism of a procedure with which I have had no experience would be presumptuous. This is not my purpose, but rather to state my reasons for not adopting it up to the present time. In my practice, one of the chief obstacles to the performance of office curettage without anesthesia would be the patient herself. If, to this lack of cooperation, one adds the frequent mechanical difficulties which render instrumentation impractical or unsafe, the number of patients in whom the procedure could be carried out becomes very limited. In this series of cases, the commonest indication for office curettage was endometrial biopsy in the course of functional studies. Granted that different portions of the endometrium do not show the same response to hormonal stimulation, I believe that in most instances this can be accomplished more safely, just as satisfactorily, and certainly more easily for both the patient and the surgeon by one of the cannulas now available.

When a diagnostic curettage is indicated, it should be performed in such a manner as to insure the maximum of safety, thoroughness, and accuracy. That these requirements can be met more expeditiously with the patient under general or spinal anesthesia in a hospital, seems to me so obvious as to require no further comment.

DR. BROOKE M. ANSPACH.—My own feelings in regard to this interesting proposal are very much the same as those expressed by Dr. Keene.

response in the endometrium, proliferation (interval phase) in 2 and hyperplasia in the remaining 1. Irrespective of the endometrial response, not one of the 10 patients bled either during or after withdrawal of treatment, again stressing the apparent independence of uterine bleeding from the presence or absence of estrogen. Another group of 9 postmenopausal women (Table II) who were also receiving large doses of estrogen for the control of constitutional symptoms did develop abnormal uterine bleeding. These observations emphasize the fact that the question of the bleeding factor in its relationship to blood-estrogen levels is not yet unequivocally clarified.

Eight regularly-menstruating women with premenstrual tension (Frank²⁵), a relatively uncommon syndrome, characterized by a cyclic alteration of personality, were curetted premenstrually. The endometrial specimens of 4 of the 8 women were of the expected secretory type but those of the remaining 4 were proliferative or hyperplastic (pseudomenstruation). Inasmuch as pseudomenstruation often results from partial or total failure of luteinization, its frequent occurrence in premenstrual tension suggests that the syndrome, in some instances, may be related to an aberration of the normal ovulatory process.²⁶

Four regularly-menstruating women with abnormal breast hyperplasia (2 with generalized hypertrophy and 2 with adenosis) were subjected to premenstrual curettage in an attempt to evaluate the probable hormonal imbalance. The endometrium of the 2 patients with generalized hypertrophy showed no signs of progestin stimulation. Furthermore, 1 of these 2 patients showed double the normal quantity of blood and urine estrogen. These findings are corroborative of the present conception that generalized hypertrophy of the breasts results from a hyperestrinemia without the modifying influence of progestin. The endometrium of the remaining 2 patients who had multiple, painful nodules in both breasts, a condition known as adenosis or mazoplasia, was of the normal secretory type. Inasmuch as adenosis is attributed to a hyperfunctional state of the anterior pituitary lobe (Mazer,²⁷ and Lewis and Geschickter²⁸), a normal progestin-stimulated endometrium should be expected premenstrually in such women.

CONCLUSIONS

1. Study of the endometrium in 305 patients who were subjected to office curettage because of menometrorrhagia, functional sterility, amenorrhea, premenstrual tension, or abnormal breast hyperplasia furnished valuable information concerning probable etiology and uncovered 5 early cases of adenocarcinoma.

2. In the series of 305 office curettements herein reported, only 2 untoward reactions, temporary in nature, occurred.

3. Office curettage, carefully performed by the gynecologist, is a safe and valuable procedure.

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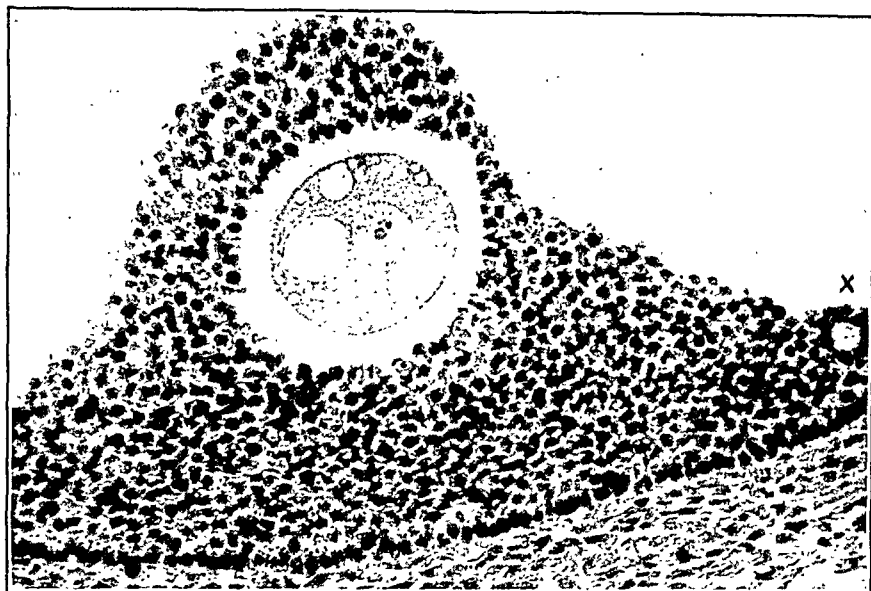


Fig. 1.—Human ovum in situ in follicle. Call and Exner body at X.



Fig. 2.—Follicles, unstimulated rabbit ovary. Call and Exner bodies.

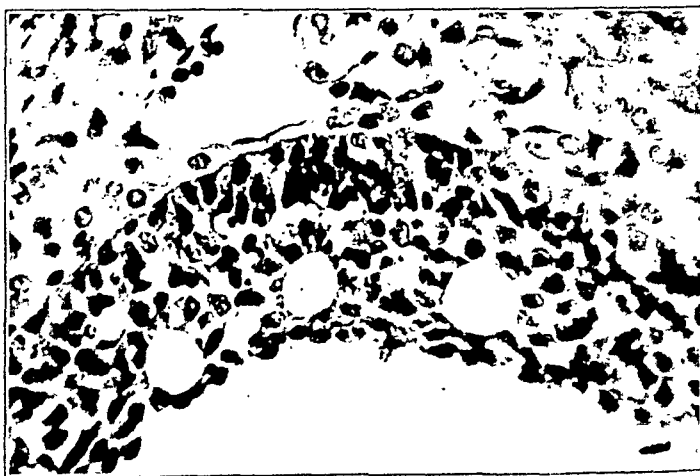


Fig. 3.—Call and Exner bodies; rabbit ovary, two hours after injection of urine of pregnant woman.

Another disadvantage of curettage as an office procedure occurs to me. When the curettings suggest malignant disease, one may, in the hospital, at a moment's notice obtain sufficient radium thoroughly to flood the endometrial cavity of the uterus with the gamma rays while the laboratory prepares rapid paraffin sections and makes a positive diagnosis. The advantages of such facilities are self-evident. Diagnostic curettage if it is to be of real value must be done thoroughly with a minimum of trauma and all aseptic precautions. I would favor the hospital.

DR. CATHARINE MACFARLANE.—I have not performed curettage in the office, nor do I wish to do so. I have done it twice in the operating room without anesthesia and regretted doing this, because the patients suffered severely and I felt at the time that I had not thoroughly curetted the uterus.

DR. ISRAEL (closing).—It is virtually impossible to persuade women with functional menstrual disorders to submit to hospitalization simply for diagnostic purposes. The possibility of accurate diagnosis in such instances is one of the major advantages of office curettage.

We are accustomed to performing diagnostic curettage, usually without anesthesia, in the Out-Patient Department of the Mount Sinai Hospital and, while we occasionally experience difficulty, we are usually able to pass the small fenestrated curette with ease. We have employed the suction-curette and have found it totally inadequate for our purposes. We do employ the Randall cannula-curette with satisfactory results. However, the cannula-curette causes as much pain and is only 2 mm. smaller than the No. 1 Sims curette.

RUPTURE OF THE GRAAFIAN FOLLICLES. II

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WITH THE COLLABORATION OF ROSE C. KETTERINGHAM, B.S.

(From the Maternity Hospital, and the Department of Obstetrics and Gynecology, Western Reserve University)

INTERESTED in the phenomenon of the rupture of ovarian follicles as exhibited in the Friedman (rabbit) pregnancy test, we undertook to follow the sequence of events by examining the ovaries every two hours after the injection of the urine from a known pregnant woman. Careful study of the follicles at these various stages soon focused our attention upon the so-called "Bodies of Call and Exner,"^{1, 2} situated among the granulosa cells in the follicle walls. It appears to us that the changes in these organs run through a definite series before the rupture, and that the "bodies" play an important part in the phenomenon. Naturally, not all of the "bodies" seen will undergo these changes. For some reason, only a few of the hundreds of follicles present are at a stage of development that will permit them to respond to the stimulus of the urine injection. Only "bodies" in the walls of these few follicles will show the changes we describe. In other follicles, the "bodies" will remain quiescent.

Fig. 1 shows a normal, ripe human follicle, cut straight through the ovum, and showing a Call and Exner body in the base of the discus.

In Fig. 2 appear ripe follicles in the unstimulated rabbit ovary. Under this low magnification, many Call and Exner bodies appear, mere white spots scattered among the granulosa cells.

In Fig. 5, the "body" appears to be freeing itself from the surrounding granulosa cells. Their nuclei are separated quite widely from the wall of the "body," and apparently there is an open moat between the "body" and the cells. This section was taken six hours after the urine injection.



Fig. 6.—Low power view of follicle eight hours after urine injection. Broken lines point to Call and Exner bodies migrating into follicle fluid.

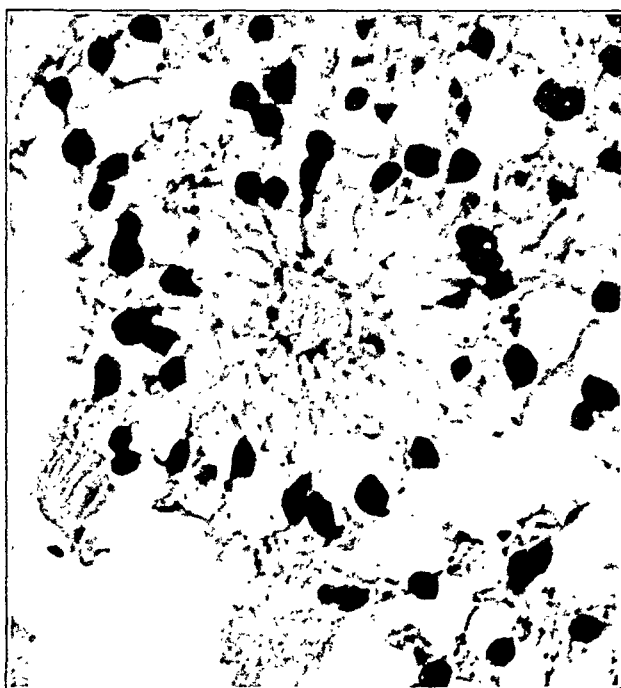


Fig. 7.—Higher power, same Call and Exner body, eight hours after injection of urine.

Fig. 6 is a low power view of a follicle eight hours after the urine was injected. Here we note that the "bodies" have cast loose entirely from the granulosa, and have moved toward the center of the follicle. Some of the surrounding cells cling to them, but have been pushed far off.

Seen under higher power, in Fig. 7, rays appear to emanate from the "body"; its margin is broken and irregular; it gives the appearance of undergoing disintegration.

Fig. 3 is a higher power view of the "bodies" two hours after the rabbit had received an injection of urine. These "bodies" appear as amorphous spots, closely surrounded with the darkly staining nuclei of granulosa cells. No reaction seems to have started as yet.

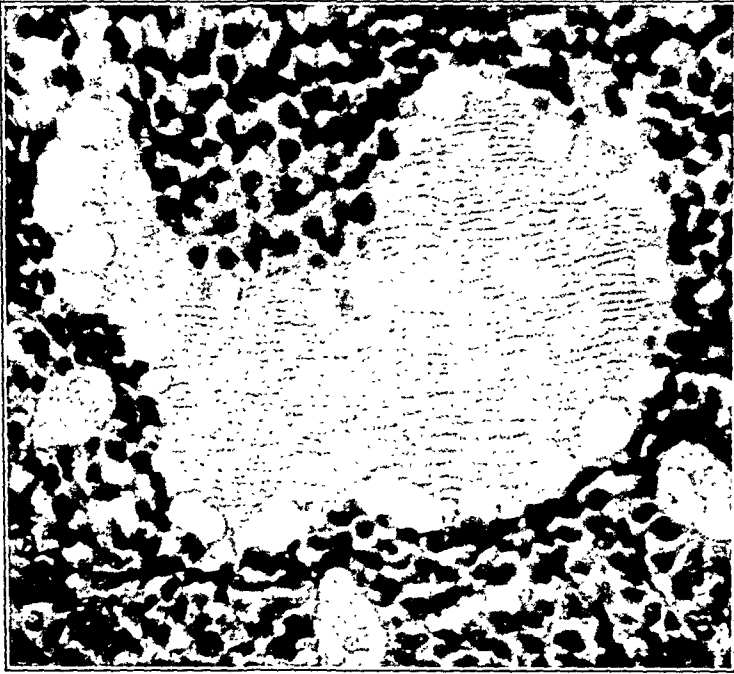


Fig. 4.—Call and Exner bodies, four hours after urine injection.

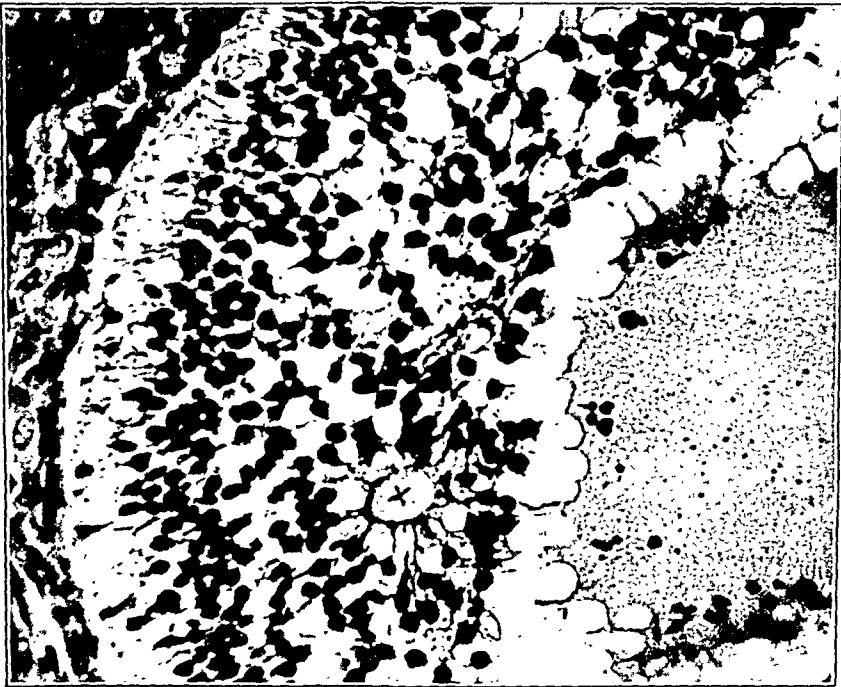


Fig. 5.—Call and Exner bodies, six hours after urine injection.

Fig. 4, taken four hours after urine injection, shows definite reticular structure in the "bodies." They appear larger, and their shape is more irregular. Granulosa cells are still packed closely around them.

ever. The cornua are unengorged; the ovaries contain only mature but unruptured follicles. The black specks on these ovaries, seen in the photograph, are merely the cut ends of vessels entering the hila. The test animal and the control were litter mates, each weighing 2.94 kg.

In a second trial, we were so anxious to avoid insulin shock that we did not get the blood sugar of the test animal below 80. The animals were opened after forty-eight hours. Both the test and the control gave strongly positive reactions.

Experiment 3 also failed because, for some unexplained reason, the control rabbit as well as the test one failed to show any reaction.

At our fourth trial, the test rabbit died in shock too soon, at the end of eleven hours. Her ovaries showed no reaction at all. There was definite engorgement of the cornua of the control. There were no ruptured follicles; but sections showed the Call and Exner body changes we have described. This phenomenon was not seen in the test animal.



Fig. 8.—On right, uterus and ovaries from rabbit which received urine from a pregnant woman, and also insulin. No Friedman reaction. On left, uterus and ovaries of control animal which received the same dose of the same urine, but no insulin. Strong Friedman reaction.

In Experiment 5, the test animal was killed after twenty-eight hours, to avoid giving glucose for insulin shock. The sugar had been kept down pretty well, ranging from 94 to 37. A previous injection of glucose for shock had shot the blood sugar to 147. Here, too, the control gave a strongly positive Friedman reaction. The test animal showed little sign of change, though there was a trace of blood in the fluid of two unruptured follicles.

Trial six was also handicapped by failure to keep the blood sugar of the test animal at a uniformly low level. Glucose had to be given to counteract shock. The rabbit was kept alive forty-eight hours. Again, the control was strongly Friedman positive. The ovaries of the test animal showed, grossly, two follicles that appeared freshly ruptured. However, slides from the control showed masses of fresh luteal tissue growing into the follicles, whereas in the test animal not a trace of corpus luteum formation could be found.

We have examined many sections from the ovaries of rabbits which have not been stimulated by the injection of urine containing the pro-lans. In none of these slides can we find any Call and Exner bodies which present the picture seen eight hours after injection.

After eight hours, no trace of these "bodies" can be found in the follicles. Has their substance been entirely absorbed into the general follicle fluid?

Now it is just about this time, eight hours after stimulation, that a follicle begins to show definite swelling; an increasing internal tension which progresses until the rupture which occurs from ten and a half to twelve hours after the urine has been administered.^{3, 4} We felt justified in adopting the working hypothesis that these dissolving "bodies" have contributed something to the follicle fluid which increases its osmotic tension so that it takes up fluid from the surrounding tissue and so increases the content of the follicle until it reaches the bursting point. Previous observations⁵ have led us to believe that there really is such an increase of osmotic tension.

What could the Call and Exner body throw into the follicle that would thus raise the fluid osmotic tension? A salt or a sugar was our first idea. So we made a rough trial-and-error guess at the possibility that the sought-for substance might be a hydrocarbon. Follicles at the various stages were sectioned and stained with Best's carmine, which is said to be specific for glycogen. The results gave evidence that there really is some increase in the glycogen content of the "bodies" as the follicle approaches rupture.

The idea suggested itself that it might be possible to keep the blood sugar so low by the use of insulin that these "bodies" could not obtain the glycogen they need to perform their rôle in the rupture of the follicle, and thus the typical Friedman reaction might be inhibited. The matter has been tried out on a number of rabbits, using each time a control which received the same dose of the same urine as did the test animal, but which did not receive any insulin. During the tests, the blood sugar of both test and control rabbits was estimated frequently. Great difficulty has been met in our effort to keep the blood sugar at a uniformly low level for a period of about forty-eight hours. Attempts to keep it down frequently resulted in hypoglycemic shock for the animal. The giving of glucose at such a time will save the animal's life at the cost of pushing the blood sugar to too high a level. Many times, the blood sugar got out of control, and rose to an almost normal figure before the fact was detected at the next sugar estimation test. A very few hours of such near-normal are sufficient to vitiate an experiment.

Test Rabbit 1 lived twenty-seven hours, finally dying in insulin shock. Its blood sugar had been held down fairly well to figures ranging from 34.7 to 50 mg. per 100 c.c. The control rabbit, receiving no insulin, ran a blood sugar between 65 and 74. Organs were removed at once, after the death of the test animal, from it and from the control. They are pictured in Fig. 8. The control specimen, on the left, shows a strongly positive Friedman reaction. There are engorgement and hyperplasia of the uterine cornua, and many *corpora hemorrhagica* are seen in the ovaries. The test animal's organs, shown on the right, present no reaction what-

2. There is evidence that these "bodies" contribute something, possibly glycogen or a sugar, to the follicle fluid. This so raises the osmotic tension of the fluid that the follicle tension is increased to the point of rupture.

3. This idea of the mechanism is supported by observations that holding down the blood sugar with insulin definitely inhibits the rupture of the follicles.

We wish to express our gratitude to Dr. Arthur H. Bill for his interest and cooperation in this work. He made it possible for us to obtain the material needed for these experiments.

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10515 CARNEGIE AVENUE

HYPEREMESIS GRAVIDARUM*

A CLINICAL STUDY OF 396 CASES

J. E. FITZGERALD, M.D., AND AUGUSTA WEBSTER, M.D., CHICAGO, ILL.

THE following report is based on the cases admitted to the Cook County Hospital during the twelve years from 1925 to 1936 inclusive. In that time 360 women were admitted to the wards because of vomiting that seemed intractable enough to require hospitalization. Of these, 29 were readmitted one or more times because of recurrent symptoms. The admission diagnosis was made entirely on the history given by the patient. Many patients were sent in from our own prenatal clinic, a certain number were referred by outside physicians, but the majority applied for admission because of their discomfort. This class of patient very rarely accepts hospitalization without good reason. No attempt was made to classify these cases as to their theoretical etiology.

Because there are no standardized criteria by means of which the seriousness of this condition may be estimated we have grouped the cases according to their hospital stay, hoping thereby at least to distinguish between those who responded readily to treatment and those who were more difficult to manage. It will be noted that nearly half of the patients were discharged in a week or less and that over two-thirds were well enough to go home by the tenth day, leaving less than one-third who were under treatment for more than ten days.

Theoretically, parity, color, and marital state may have some importance as etiologic factors in this condition. It has been stated that the disease does not occur in full-blooded negroes, and while many of our colored patients are not pure stock, nevertheless they accounted

*Presented at a meeting of the Chicago Gynecological Society, October 22, 1937.

In our seventh attempt, four rabbits were used. One was the control. We gave what, on the basis of the weights, we estimated to be about 1, $2/3$ and $1/2$ lethal doses of insulin to the three test animals. The rabbit receiving the heavy insulin dosage went into hypoglycemic shock frequently, and had to be rescued with glucose injections. These sent the blood sugar readings so high at times that they may explain the final atypical reaction in the ovaries, where some blood was found in one unruptured follicle. The other two rabbits showed no reaction, though the control gave the definite picture of a twenty-four-hour positive Friedman test. All the animals were opened twenty-four hours after the first urine injection because Rabbit 1 died in shock at that time.

Thus we come to believe that the sugar metabolism is an important factor in ovulation. Hyperglycemia may operate, as well as hypoglycemia. Diabetics are notoriously infertile. May it not be that, in them, the blood sugar raises the osmotic tension outside the follicle to a point so high that the contributions of the Call and Exner bodies are unable to concentrate the follicle contents to a point where fluid will pass in from the surrounding tissues?

It was suggested that a rabbit with a blood sugar reduced to about 50 is a rather ill animal. May it not be that, with its metabolism so low, many physiologic processes, such as ovulation, are inhibited? If its vitality were reduced by means other than insulin, might not the result be the same? In order to answer these questions, a rabbit, injected with urine from a pregnant woman, was twice reduced to the point of collapse by bleeding; once from the jugular, and once by needling the ventricle. In spite of this shock, the ovaries, at the end of forty-eight hours, showed a strongly positive Friedman reaction.

The blood sugar determinations were made by the micromethod of Folin and Malmros as modified for small amounts of blood by Jeghers and Myers.⁶ The technique was standardized as far as possible by having all blood collected and all tests run by the same person; satisfactory checks were obtained in practically all tests.

The ear of the rabbit was shaved to expose the marginal vein, which was punctured with a Hagedorn needle to obtain the sample. The rabbits bled freely from such punctures, and in most instances enough blood (50 c.mm.) was obtained for duplicate determinations. Occasionally the same puncture could be used for determinations at intervals of several hours by scraping off the small clot which formed following cessation of bleeding. Rabbit blood clots more quickly than that of human beings, especially if it comes in contact with fur, so it was necessary to shave a considerable area. Precautions in cleaning the ear were also of some importance, especially following the injection of 50 per cent glucose, since relatively small contaminations affect the validity of this sensitive test.

The normal fasting blood sugar for human beings by the Folin-Malmros modified test ranges from 70 to 90 mg. per 100 c.c. We have not determined the normal fasting blood sugar of rabbits by this method, since we were not primarily interested in this problem. As our animals were not uniformly fasted either before or during the tests, our figures represent only the determination for an individual rabbit at the time of test. Regardless of the blood sugar value at the beginning of the test, the majority of animals went into shock with values of 30 to 40 mg. per 100 c.c., although some individual differences were evident, just as in tolerance of insulin.

CONCLUSIONS

1. In the process of ovulation, in rabbits, the Call and Exner bodies of the follicle walls undergo characteristic alterations, and migrate toward and into the follicle fluid, where they disintegrate.

but in the succeeding charts, they are divided into those who were considered cured at the end of ten days and those who were uncontrolled by that time.

Admission Findings.—All of these patients were admitted because of persistent vomiting. The majority complained of abdominal or epigastric pain. It will be noted that of those who were able to leave the hospital in ten days approximately one-third showed abnormal pulse and temperature on entrance. Nearly half of them showed acetonuria. Such findings were definitely more common in the group whose symptoms were harder to control.

TABLE III. ADMISSION FINDINGS

	10 DAYS OR LESS	OVER 10 DAYS
Total cases	280	116
Pulse 100 plus	95	67
Temperature 99° F. plus	92	50
Urinary Findings		
Albumin	46	30
Acetone	135	71
Diacetic acid	40	29

TABLE IV. TREATMENT

	10 DAYS OR LESS	OVER 10 DAYS
Total cases	280	116
Glucose		
None	165	43
100 or less	85	34
Over 100	30	39
Saline		
None	165	43
5,000 or less	102	50
Over 5,000	13	23

Treatment.—Hyperemesis is a disease whose true etiology is obscure. Consequently the treatment has been mostly empirical, and the varieties thereof have been almost endless. These patients suffer from dehydration, starvation acidosis and damage to the parenchymatous organs, notably the liver. Obviously no one can suggest a treatment which fits every case or any individual case. Titus and Givens, in 1923, made certain suggestions that have proved generally helpful. They believed that these patients suffered from dehydration, loss of glycogen storage, toxic damage to the liver and possibly other organs. Experimental studies had proved that the liver of laboratory animals would withstand toxic doses of metallic poison such as phosphorus, provided the animal was given intravenous glucose as a buffer. They also showed that liver tissue damaged by such drugs as phosphorus or chloroform would regenerate with great rapidity in the presence of an excess of glucose in the blood stream. They suggested that hyperemesis, being a toxic process, would be benefited by the use of intravenous or subcutaneous glucose, because (1) fluids would be replenished, (2) the liver glycogen would be restored, (3) glucose would protect the liver from damage by toxin, and (4) glucose would enable the liver to repair its damaged areas more rapidly.

The patients here reviewed were treated individually by individuals. Practically every known form of treatment was utilized. Two general principles were agreed upon by the various staff members. One was that the use of fluids and glucose constituted a most valuable adjuvant to any other method of treatment. The other was that for the first twenty-four hours these patients should have nothing by mouth and be given proctoclysis of 5 per cent glucose in saline solution. Many of these patients showed prompt improvement with rest in bed, dietary restriction and rectal

TABLE I

Total number of patients	360
Number of admissions	396
ADMISSIONS	NO. OF PATIENTS
<i>Re-Entries:</i>	
2 X	23
3 X	5
4 X	1
<i>Days in Hospital:</i>	
7 or under	191
8-10	89
11 or more	116

for almost one-third of the patients. Similarly hyperemesis is supposed to be more common in unmarried patients. In this group they accounted for 10 per cent of the total, and this is about the same ratio as the unmarried group bears to the whole clinic. Two-thirds of our patients were multigravidas, and this is about the percentage of multigravidas in the entire clinic.

The diagnosis of this condition presents no difficulty. Many of the cases were very mild, but because of home responsibilities these patients object to hospitalization, and we are convinced that the diagnosis of

TABLE II. CLASSIFICATION OF PATIENTS

	NO. OF PATIENTS
Colored	117
White	212
Not recorded	28
Mexican	2
Japanese	1
Primigravidas	102
Multigravidas	248
Not recorded	10
Married	325
Single	35

hyperemesis was justified whenever they were willing to enter the hospital for treatment. No attempt was made to group them in accordance with the probable etiology of their symptoms. We have no record of any case which was relieved by the correction of local conditions, such as uterine malposition or cervical pathology. Our experience with the so-called neurotic vomiting has convinced us that whether or not neurosis may be the cause of severe vomiting, the health and even the life of the patient depend upon one's ability to control the symptoms. It is our belief that these patients would be better served if they were divided into two groups: (1) Those who improve promptly on proper management, and (2) those whose symptoms and findings persist in spite of adequate treatment. The patients in the first group are never in any danger. Those in the second group are always potential fatalities. No attempt is made to group the subjects of this report in this manner

Deaths.—Hyperemesis is a disease which should never result fatally unless the patient is fatally damaged when first seen. The occurrence of 15 deaths, even in a large series of cases and over a long period of time requires comment and explanation if we are to eliminate this disease as a factor in maternal mortality.

Of the 15 fatal cases in this group, four patients entered the hospital for the first time with such marked damage that there was never any possibility of help from any method of treatment. Two of them entered with a pulse over 120, temperature over 101° F. Both were irrational. Both had involuntary urination and defecation. One died in fifty hours, the other early in her fourth hospital day. Two patients entered with definite peripheral polyneuritis. One of these had been treated for four weeks in another hospital and was transferred to us because she had become irrational and had visual and auditory hallucinations. She had stopped vomiting and was taking food by mouth. Because of this apparent improvement relatives refused permission to empty the uterus. In spite of large quantities of glucose and fluid the patient became worse, and permission to empty the uterus was obtained on the fourth day. There was no improvement, and the patient died on the ninth day. The other patient with polyneuritis was aborted on the third day, but in spite of this and generous quantities of fluid and glucose she died on the eleventh day. These 4 patients entered the hospital too late for treatment.

One patient was treated in a medical ward for eight days as a pelvic peritonitis. She was then transferred to us with a pulse of 124, temperature 99° F., albumin, acetone and diacetic acid in the urine. This patient was treated medically for fourteen days, during which time she received 400 gm. of intravenous glucose, 100 gm. of subcutaneous glucose and 16,400 c.c. of saline. In spite of the fact that her temperature remained normal, her pulse remained well over 100, and her urine continued to show acetone and diacetic acid. She was becoming listless and uncooperative and the uterus was emptied on the twenty-second hospital day. Treatment was continued, but there was no response. She died on the thirty-second day. This patient, we feel, could have been saved by earlier abortion.

One other patient entered with normal temperature, pulse of 104 but with albumin, diacetic acid and acetone. On the third day casts appeared in the urine. On the fourth day a bag was inserted (she was four months pregnant). In spite of generous quantities of glucose and fluid, she continued to get worse. On the sixth day she was irrational and on this day she expelled the fetus. She died on the ninth day. The lack of promptness in aborting this patient is open to criticism.

Nine of the 15 deaths are of particular interest, because the patients had been in the hospital previously during their current pregnancies. Seven of these had been in the obstetric ward because of vomiting. Four left the hospital on their own responsibility. One returned after seventeen days in terminal condition, bleeding from the nose and mouth; red cell count was 1,100,000, pulse 130, temperature 101.8° F. Dilatation and curettage were done on the third day and the patient died on the fifth day.

Two others of this group re-entered after twelve days. One was retaining food and fluids but was listless, sluggish, and uncooperative. On the eighth hospital day she became irrational, and the uterus was emptied. She died ten hours later. Earlier abortion might have prevented this fatality. The other patient who returned in twelve days received the usual intensive treatment and on the seventh day was thought to have a pneumonia. The uterus was never emptied, and she died on the seventeenth day. This death should have been preventable. The last of this group re-entered after eight days. She had an active gonorrhea, which made the wisdom of a therapeutic abortion questionable. In addition to this she was in a ward reserved for the treatment of venereal disease, and the seriousness of her toxemia was underestimated. Therefore, the severe vomiting was allowed to continue almost without treatment. By the fifth day she had become irrational, but she had stopped vomiting. The next day she was able to retain food, but she was stuporous and irrational. She died on the fifteenth day. It seems reasonable to believe that this patient could have been saved by early and proper treatment.

feedings. Of those who remained ten days or less, practically 60 per cent had no further treatment, and of those who were not discharged in ten days, 40 per cent recovered on gastric rest and rectal feedings. The majority of these patients was readily controlled, and it is common knowledge that hospitalization and complete absence of visitors result in prompt improvement in most cases. In the more resistant cases, more strenuous treatment must be instituted. In this type of case, generous quantities of fluids and glucose were added to whatever other treatment the attendant deemed proper in the individual case. The additional fluid was normal saline solution given intravenously or subcutaneously. Glucose was given either in a 5 per cent solution subcutaneously or in 25 per cent solution intravenously. The general extent of this treatment is indicated in the chart. Obviously patients with more or less easily controllable symptoms received less intensive treatment. In the second group a third of the patients got more than 100 gm. of glucose contrasted to 10 per cent in the first group. Likewise 20 per cent of the second group were given more than five liters of fluid compared to less than 5 per cent of the first group.

The extent to which this treatment was carried in an effort to preserve the pregnancy and at the same time prevent harm to the mother can be illustrated by one case. This patient was a primigravida, aged 23 years, who entered in the fourth week of her pregnancy. On entrance she was referred to surgery as an intestinal obstruction because of abdominal distention with a history of incessant vomiting for ten days. After ruling out an obstruction she was transferred to obstetrics. On admission to our service the patient showed a pulse of 104 and a temperature of 99.8° F. Acetone and diacetic acid were present in the urine. The diagnosis was evident, but because she had taken ergot in an attempt to abort herself, the presence of a psychoneurosis was admitted as an etiologic factor. Treatment was instituted at once. During the next forty-three days fluids and glucose were given either subcutaneously or intravenously on thirty-four days. During that time this patient received 39 liters of subcutaneous saline. In addition she received 18 liters of 5 per cent glucose subcutaneously and 1,600 gm. of glucose in 25 per cent solution intravenously. Nevertheless her vomiting had not entirely ceased until the fortieth day, and acetone was present in the urine almost constantly for the same length of time. Her improvement was gradual thereafter and she was not discharged from the hospital until the seventy-fifth day. She was subsequently delivered of a normal infant at term.

TABLE V. ABORTIONS

Spontaneous	4
Therapeutic	32
Recovered	23
Died	9

TABLE VI. FATALITIES

Deaths	15
Pregnancy interrupted	9
Pregnancy not interrupted	6
Re-Entries	9
Discharged from OB as improved	3
Signed release	4
Discharged from Medical Service	2
Entered in terminal state	2
Entered with polyneuritis	2
Additional cases	2

Abortion.—In spite of treatment a certain number of these patients failed to improve. Thirty-two were subjected to therapeutic abortion. Of these, 23 recovered promptly and were discharged well. Nine died even though the uterus had been emptied. The details of these cases will be reported in the study of the fatalities of the series.

6. Ability to retain food and fluids in seriously ill patients is not necessarily a sign of improvement.

7. Deaths from hyperemesis are avoidable.

8. The majority of this group responded promptly to rest, diet, glucose therapy, and fluids.

9. Those that fail to respond to adequate treatment in a reasonable length of time should be aborted.

10. Therapeutic abortions delayed too long are not life-saving measures.

104 SOUTH MICHIGAN AVENUE

30 NORTH MICHIGAN AVENUE

DISCUSSION

DR. FREDERICK H. FALLS.—There are several special types of this disease. One group which was not mentioned presents symptoms of hyperthyroidism. We have had a considerable number of these cases showing basal rates varying from plus 111 to 140. These patients have lost a great amount of weight, have a fine tremor, a pulse of 120, and enlargement of the thyroid. They are the women who if they were not pregnant would be diagnosed Graves' disease. If you give these women Lugol's solution, 10 drops, three times a day throughout pregnancy, the vomiting is controlled. These cases have been seen in consultation by men skilled in thyroid surgery, who have made a diagnosis of hyperthyroidism and advised thyroidectomy. They have believed that such patients would improve over a short period of time and then, if not operated upon, would develop a thyroid crisis. In pregnancy, however, under medical management this does not occur. One woman for instance took Lugol's solution from September 26 until February 3, when she was delivered. Her thyroid symptoms subsided almost immediately. She was then sent to the same surgeon who had advised thyroidectomy during her pregnancy, but he now could find no need for an operation.

There is a group also due to intestinal obstruction, especially following an appendectomy with drainage. One woman of 23 years had had an appendectomy with drainage at the age of nine years. She became pregnant two years ago and had to be aborted because of the hyperemesis. She became pregnant again this year and developed all the symptoms of hyperemesis gravidarum plus the symptoms of partial obstruction. When she came to us the question was whether we should attempt to enter the abdomen and relieve the obstruction in the presence of severe hyperemesis, jaundice, dehydration, and with diacetic acid in the urine, or empty the uterus again. We felt we did not dare to subject her to this risk and instead emptied the uterus.

I would like to re-emphasize what Dr. Fitzgerald said about polyneuritis and also about mental symptoms. I remember one patient with severe hyperemesis, who was found wandering about the halls at night slightly irrational. We later did a vaginal hysterotomy under local anesthesia. She lost about two ounces of blood, but her pulse went from 160 to 210. We returned her to bed and gave hypodermoclysis. Her pulse came down to 160 but she died on the second day. We had a complete post mortem except the thyroid and that was not thought to be important at that time. The pathologist could not tell us from what this woman had died. The liver and kidneys failed to show the usual degeneration said to be characteristic of this disease.

After emptying the uterus many of these patients are not saved. In two other instances on my service in Iowa, the patients lived a month after the uterus was emptied. One patient was taking an adequate diet but she died of toxemia. The other patient continued to vomit for a month and died. I feel there are things about this disease that are not understood, and that some of these cases are associated with hyperthyroidism.

Three patients had been released from the Obstetrical Wards as improved or cured. One returned in fifteen days in terminal condition and died in forty-eight hours. Another returned in twenty-eight days and died in thirty-six hours. The other returned in nine days, with a pulse of 150, temperature 101° F., albumin, acetone and diacetic acid. She was aborted on the seventh day and died on the tenth. It is evident that these patients were not cured when they were allowed to leave the hospital on their previous visits. Of the two who were released by the medical service, one was discharged as pregnancy with cholelithiasis and given dietary management. She returned in seventeen days vomiting but with negative urine, a pulse never over 120 at any time. She developed periods of irrationality and the vomiting was persistent in spite of negative laboratory findings. She was not aborted until the twenty-first day and she died on the twenty-second. The other was discharged as a duodenal ulcer because of a previous history. She was sent back to the hospital nine days later by the prenatal clinic, but her vomiting was slight and she was considered a threatened abortion. Her pulse remained around 120 but her temperature and urine were normal until the fifteenth day. On the sixteenth day she was curetted by the resident on the Obstetrical Service and a loop of bowel was pulled out through a perforation in the uterus. She died on the operating table in an attempt to repair the damaged bowel.

COMMENT

Consideration of a large number of cases of hyperemesis reveals that they may be placed in two groups for prognostic study. The first group improves readily, often with no treatment except rest and isolation, and the life of the patient is never in jeopardy. The smaller second group responds slowly to treatment and is responsible for a small number of maternal deaths. The deaths from this disease could be decreased by a more widespread recognition of its potential seriousness. A study of the fatal cases of this series indicates that a certain number of deaths might have been prevented, and that they can be prevented in the future by close attention to some general principles:

1. The so-called cured patients should be kept under close observation.
2. The lack of clinical improvement, regardless of laboratory findings should be regarded as a bad prognostic factor.
3. Likewise, apparent clinical improvement such as cessation of vomiting and ability to retain food, in the presence of persistent tachycardia, elevated temperature and persistent urinary abnormalities, may give one a false idea of the patient's improvement. In 6 of the 15 fatal cases the patients were retaining food for some time before death.
4. Listlessness, stupor, involuntary urination and defecation, and periods of irrationality are frequently evidence that the toxemia will result fatally whatever the treatment.
5. The use of cervical packs, bags, etc., is not recommended in cases where therapeutic abortion is to be done. If the cervix is not easily dilatable, vaginal hysterotomy should be done so that the uterus may be emptied promptly.

SUMMARY

1. Three hundred ninety-six cases of hyperemesis are reviewed.
2. There are 32 therapeutic abortions.
3. There were 15 deaths in this series.
4. Color, age, parity, and marital state seem to have no influence on the course of the disease.
5. Persistent tachycardia, fever, diacetic acid, and acetone are danger signals.

found in 25 per cent of pregnant women at term by cultural methods. Recent literature reveals only a few articles, and most of our textbooks pay little attention to vaginal mycosis, thus explaining the paucity of observations on the incidence of fungi in the vagina.

Too little attention has apparently been shown toward the possible source of oral thrush in the infants from mothers infected with mycotic vaginitis. Haussmann² demonstrated, immediately after birth, spores in the mouths of children born of mothers with vaginal mycosis. Noack, Faber and Clark, and Cron⁶ have all stated the possibility of oral thrush being due to genital infection of the mother. More recently Crossen⁷ pointed out that a mother might infect herself, and a vaginal mycosis result from her thrush-infected baby. DeLee⁸ states that one may have a yeast vaginitis which resembles oral thrush. Very few authors have called attention to the danger of infection of the newborn by the yeast infection of the mother. Hesselstine, Borts, and Plass⁶ proved by experimental inoculation that the fungi present in the vaginas of pregnant women can produce oral thrush. This has been confirmed recently by the excellent study of Bland, Rakoff, and Pincus.⁹

PROCEDURE

Research work was carried out in the Chicago Lying-in Hospital and the Stock Yards dispensaries. The patients who attend the hospital clinic are of a definitely better economic class than those in the Stock Yards clinic. In the latter, the patients were segregated into two groups, white and colored, while at the former no colored patients are accepted. Cultures were taken as routinely and consecutively as possible, being only interrupted by certain unavoidable factors. Each patient was asked about the presence of genital symptoms and observations were made on the amount of vaginal discharge and clinical appearance. A culture was then taken from the vagina with a sterile swab and implanted on Sabouraud's media, the cultures incubated for twenty-four to forty-eight hours and then read.

In the study of oral thrush in the babies, the charts were reviewed from the opening of the new Lying-in Hospital in May, 1931, up to Oct. 31, 1936. Undoubtedly some records of babies with oral thrush were missed in this review, especially those for the earlier years. The clinical diagnosis was confirmed in each case by direct smears and/or culture. Then the records of all mothers of babies with oral thrush were reviewed to check the relationship of the possible mother's infection to the baby's thrush. In addition to the above groups, there was a similar study on 47 mothers with positive culture for fungi and on their 47 babies.

DISCUSSION

In Table I we quote the further unpublished results of Plass, Hesselstine, and Borts which were presented in the Scientific Section Exhibit at the American Medical Association convention in Philadelphia in 1931.

TABLE I

PREGNANT PATIENTS	YEAST	
	PRESENT	ABSENT
(No symptoms) 184	60 (32.6%)	124 (67.4%)
(With symptoms) 48	27 (56.25%)	21 (43.75%)

These authors found that among the 232 pregnant women studied, yeast organisms were found by culture and/or smear in 87 patients, a total incidence of 37.5 per cent. Of this positive group only 27, or 11.63 per cent, of the total had symptoms and evidence of a vulvovaginitis. Of the 87 pregnant patients who had positive evidence of mycosis 27 (or 32 per cent) had symptoms.

DR. EDWARD L. CORNELL.—In the management of these cases, we often forget that vitamin B and other vitamins are necessary to prevent polyneuritis. Vitamin extracts should be included in the diet.

Many of us neglect also to use the Levine tube for feeding these patients. You can often succeed in getting food in the duodenum by this means.

Glucose, 10 per cent solution, should be given in amounts of at least 3,000 c.c. intravenously in the first forty-eight hours. After that, if the toxicity is diminishing, the 5 per cent solution will be adequate.

RELATIONSHIP OF ORAL THRUSH TO VAGINAL MYCOSIS AND THE INCIDENCE OF EACH

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THIS study was undertaken to determine the relationship of the sporadic cases of oral thrush in the newborn to vaginal mycosis in the mother, and the general incidence of each. This work was stimulated by the lack of adequate data supporting the views expressed in the literature. A series of routine vaginal cultures on 402 women in the third trimester of pregnancy was taken to determine the incidence of fungi. Also a series of 90 babies with positive oral thrush was studied with relationship to mycoses in their mothers. It will be shown later that the incidence of fungi in the genital tract of the mothers appears to be associated with the hygienic level, further that the babies born of such infected mothers have about a thirty-five times greater chance of developing oral thrush than infants born of noninfected mothers.

For a rather complete review of the literature the reader is referred to the study by Plass, Hesseltnine, and Borts¹ on "Monilia Vulvovaginitis."

The reported incidence of yeast vaginitis varies; Haussmann² in 1875 reported that 11 per cent of women in late pregnancy harbored the organism without symptoms; v. Winkel³ in 1866 found six cases of mild infection among 150 women, an incidence of 4 per cent; v. Herff⁴ noted 24 cases of acute, and subacute mycotic vaginitis among 13,283 admissions, an incidence of only 1 in 553, and of these 15 occurred among 2,010 pregnant women (1 in 134) while the remaining 9 occurred among 11,273 gynecologic patients (1 in 1,252). The last author excluded from his series, however, those patients who showed obvious evidence of mycotic vaginitis, as determined by the presence of thrushlike patches on the vaginal mucosa. In the study of 63 patients with symptoms, by Plass, Hesseltnine, and Borts,¹ 18 were pregnant, and 45 nonpregnant; an incidence of 66.7 per cent was found in the pregnant group, and an incidence of 24.4 per cent in the nonpregnant group. In a control series of 85 patients without symptoms of irritation, among 46 pregnant patients an incidence of 32.6 per cent was found, while in 39 nonpregnant women the incidence was 15.4 per cent. It was concluded that economic status did not influence the occurrence, and that the increased percentage among the pregnant patients was partially explained by the known preference of mycotic organisms for an acid media, which is present in the vagina in pregnancy. Stander⁵ quotes that "yeasts" were

TABLE III. THE INCIDENCE OF ORAL THRUSH FOR EACH FISCAL YEAR OF THE HOSPITAL

YEAR	NO. CASES OF ORAL THRUSH
5/25/31 to 6/30/31	0 (?)
7/ 1/31 to 6/30/32	1 (?)
7/ 1/32 to 6/30/33	6 (?)
7/ 1/33 to 6/30/34	17
7/ 1/34 to 6/30/35	22
7/ 1/35 to 6/30/36	39
7/ 1/36 to 10/31/36	5
5½ years	90 cases

TABLE IV. THE INCIDENCE OF ORAL THRUSH IN THE NEWBORN

	NUMBER	NO. ORAL THRUSH	INCIDENCE
Babies born	14,640	90	0.6%
Mothers with known vaginal mycosis	47	10	21.0%

From Table IV, therefore, one may conclude that a baby born of a mother with known vaginal mycosis has approximately a 35 times greater chance of developing oral thrush than a baby born of a mother without a known mycosis in the Chicago Lying-in Hospital.

TABLE V. DATA CONCERNING THE MOTHERS OF THE 90 BABIES WITH ORAL THRUSH

Mothers with positive yeast cultures (genital)	22
Mothers with negative yeast cultures	27
Mothers with no cultures taken	41

Among the mothers of these thrush-infected babies, it was found that 49 had been studied either ante partum, post partum, or both (Table V). Of these 49 mothers 22, or 44.89 per cent, were found to have positive evidence of vaginal mycosis, while 27, or 56.11 per cent, had no demonstrable evidence of the infection.

TABLE VI. DISTRIBUTION OF THE BABIES WITH ORAL THRUSH TO THE NURSERIES

	CASES OF THRUSH	AVERAGE NO. BABIES IN NURSERY (PER DAY)
Second floor nursery	10	15
Third floor nursery, south	45	25
Third floor nursery, north	25	25
Fourth floor nursery	8	12
Isolation nursery	2	8

The time at which the cases of oral thrush developed was noted also. These factors could not be determined accurately in some of the earlier cases, so that they were omitted in forming the following conclusions. Of 66 cases of thrush among approximately 6,130 babies, 43 were probably endemic, and 23 were questionably contracted by contagion in the nurseries. Thus, we might say the incidence of thrush to all babies in this series is one in 92, or 1.07 babies out of 100 will have thrush.

The findings in our series of 402 women who were examined during the third trimester of pregnancy for evidence of vaginal mycosis are shown in Table II.

TABLE II

CASES	LOCATION		POSITIVE { SMEARS CULTURES		NEGATIVE { SMEARS OR CULTURES	
100	Stock Yards Colored	With symp.	17 (17.0 %)	41.0 %	5 (5.0 %)	59.0 %
		Without symp.	24 (24.0 %)		54 (54.0 %)	
150	Stock Yards White	With symp.	25 (16.66%)	33.33%	5 (3.33%)	66.66%
		Without symp.	25 (16.66%)		95 (63.33%)	
152	C.L.I.H.	With symp.	8 (05.26%)	14.47%	5 (3.28%)	85.52%
		Without symp.	14 (09.21%)		125 (82.89%)	

The three groups of patients have been reviewed separately because of their different hygienic standards. The white and colored groups from the Stock Yards clinic are almost entirely indigent patients from the lower classes, while the Lying-in series of 152 cases are from a much better hygienic and social state. Of these groups, the indigent colored group shows a total incidence of 41 per cent, and the indigent white group an incidence of 33 per cent, while the nonindigent, or Lying-in group, shows an incidence of only 14 per cent. This apparently contradicts some earlier voiced opinions as to the influence of the economic level and personal hygiene of the patients. Taking the total number of patients with vaginal mycosis, regardless of class, which is 113 out of the series of 402 cases, the total incidence is 28 per cent. Of the 113 patients with positive evidence of mycosis, only 50 had symptoms of a vulvovaginitis, or 12.4 per cent of the total group. Or, on the other hand, 50 of the 113 patients with evidence of mycosis had symptoms, an incidence of 44.2 per cent.

Of the babies born to 152 women in the Lying-in group, 3 developed oral thrush, all three mothers having had positive cultures for vaginal mycosis; thus in this series the incidence of oral thrush was 1.98 per cent. Here 100 per cent of their mothers had vaginal mycosis.

Among 44 mothers not studied elsewhere who had positive evidence of vaginal mycosis, 7 babies developed oral thrush, or 15.9 per cent. Adding the above three mothers to the latter 44, a total of 47 positive mothers showed an incidence of oral thrush in their babies amounting to 21 per cent.

From the opening of the present hospital on May 25, 1931, until Nov. 31, 1936, among approximately 14,640 babies delivered, 90 babies developed oral thrush (Table III). Thus, approximately 1 baby among 162 developed oral thrush in our entire service, an incidence of 0.6 per cent. Some records of cases of oral thrush may have been missed during the earlier years.

PULMONARY TUBERCULOSIS IN AN ACTIVE OBSTETRIC SERVICE

WITH AN ANALYSIS OF 15 CASES

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IN THE past several years much has been said and written of pregnancy and parturition associated with pulmonary tuberculosis, especially in regard to whether or not these physiologic functions have any ill effect on tuberculous women. Most, if not all, of the reported statistics have emanated from various tuberculosis sanatoria. This analysis was undertaken with the view of presenting the role of pregnancy and parturition in pulmonary tuberculosis from the standpoint of an active obstetric service in a general hospital.

In a study of 19,634 consecutive deliveries in St. Catherine's Hospital from Jan. 1, 1918 to Dec. 31, 1935 there were found to be 15 associated with pulmonary tuberculosis, an incidence of one in every 1,309 deliveries.

As shown in Table I there were 11 cases of active pulmonary tuberculosis as evidenced by history, physical signs, positive sputum, x-ray findings, and clinical course.

TABLE I. CASES OF ACTIVE TUBERCULOSIS

CASE	AGE	PARITY	TYPE OF DELIVERY	HOURS IN LABOR	KNOWN DURATION TB. PROCESS AT TERM	POST-PARTUM COURSE	FOLLOW-UP
1	33	iii	Prem. 7 mo. Ret. placenta	4	Developed post partum	Died 18 days p.p.	-
2	26	ii	L.O.A. low forceps	10	3 years	Normal	Unknown
3	25	iv	Spont. L.O.P. P.P. hem.	10	3 months	Febrile	Unknown
4	31	v	Spont. R.O.A.	12	Discovered at term	Died 3 weeks p.p.	-
5	27	i	Premature 7 mo.	5	1 year	Febrile	Died 2 mo. p.p.
6	33	ii	Spont. R.O.A.	4	Developed p.p., old tb. hip	Febrile	Died 2 years p.p.
7	27	i	Spont. R.O.P. Ret. placenta	9	6 months	Febrile	Died 3 mo. p.p.
8	32	i	L.O.A. low forceps	4	6 months	Died 6 days p.p.	-
9	21	i	Spont. L.O.A.	17	Developed p.p.	Febrile	Unknown
10	34	v	Spont. L.O.A.	3½	3 months	Febrile	Died 3 mo. p.p.
11	23	i	Low forceps R.O.A.	8	Discovered at term	Died 1 hour p.p.	-

In Table II there are shown 4 cases of inactive or chronic pulmonary tuberculosis as determined by history, physical signs, negative sputum, x-ray findings, and clinical course.

CONCLUSIONS

1. The incidence of fungi in the vagina of women in the third trimester of pregnancy is 28 per cent.

2. The incidence of fungi in the vaginal tract appears to be related to the economic level and personal hygiene of the patient; indigent colored patients show an incidence of 41 per cent, indigent white patients an incidence of 33 per cent, while the more hygienic class of white patients shows an incidence of only 14 per cent.

3. The incidence of oral thrush in the newborn shows a definite relationship to the presence of fungi in the generative tract of the mother. At the Chicago Lying-in Hospital a baby born of a mother harboring fungi in the vagina has about a 35 times greater chance of developing oral thrush than a baby born of a noninfected mother.

4. Among 14,640 consecutive babies delivered at the Chicago Lying-in Hospital the incidence of oral thrush was found to be 0.6 per cent. However, in the last 6,130 babies of this total number the incidence of oral thrush was about 1 per cent. This apparent increase we feel is only the result of more careful observations.

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Main consideration in the treatment of puerperal sepsis is removal of the septic focus through exposure and drainage or through extirpation of a suppurating organ. The localization of such foci constitutes the real problem in treatment of puerperal sepsis. Vein ligation is seldom indicated. It is to be considered only in cases in which sepsis is of thrombophlebitic origin. The operation of vein ligation is technically not difficult; the real difficulty lies in the uncertainty of its indications. Hysterectomy is not indicated in treatment of sepsis. The only exceptions to this rule are gas bacillus infection of the uterine musculature and, occasionally, an infected myoma or abscess of the uterine wall in the course of the puerperium. These complications, however, are unusual. Hysterectomy is likewise to be considered in certain cases of life-threatening hemorrhages developing in the course of a febrile puerperium or due to retained placental tissue.

J. P. GREENHILL.

study of the obstetric histories of tuberculous women, formerly patients at Trudeau Sanatorium, find that pregnancy is definitely harmful, and Hill herself admits that the greatest mortality is found among the cases diagnosed after the termination of their pregnancy and the least in those known to have tuberculosis before the onset of pregnancy. In evaluating these reports it must be remembered that practically all of these cases are sanatorium patients, that the pregnancy occurred during the course of a known pulmonic lesion and that most of them received at least some sanatorium treatment. When we consider that 53 per cent of the cases in St. Catherine's, an average-sized general hospital with a large and active obstetric service, did not manifest themselves until term and that the known mortality was 47 per cent, and if we multiply these figures by the number of similar general hospitals throughout the country with undoubtedly the same experience, we will obtain results greatly at variance with the above reports. It would seem, therefore, the proper conclusion to be drawn from the above reports is that the prognosis of properly treated cases has improved and not that pregnancy per se has no ill effect on tuberculous women.

Most authorities are in agreement that the most dangerous periods for these women are during labor and the puerperium. The exact reason for this seems somewhat obscure. Certainly, however, the strain of labor with its attendant trauma and blood loss must play some part. It was formerly believed that the descent of the diaphragm with resultant sudden decompression of the pleural cavity at the end of the second stage of labor was the cause of flareups, but Jameson,⁸ in his exhaustive review of the literature of the entire subject states that this theory is untenable as the result of recent studies of the intrapleural pressure before and after delivery. He believes that the extension of the tuberculous process during labor or the puerperium is due to the increase of capillary permeability which is known to occur at this time.

It is well agreed that pulmonary tuberculosis per se has no effect on labor. The cases in the present series are in accord with this.

As regards the treatment of this condition, the profession is beginning to take a more definite stand. Formerly it was common practice to abort pregnant women as soon as the pregnancy was discovered.

This practice continued in vogue until 1926 when Bridgman and Norwood⁹ in reporting a series of 134 cases of tuberculosis in pregnancy found that in those cases where therapeutic abortions were performed 57 per cent died within a year after abortion. They concluded that therapeutic abortion has no place in the treatment of this condition and state "operative procedure in the presence of an active pulmonary lesion is followed by a higher mortality rate than if expectant therapy alone is employed." Barnes and Barnes in a study of 42 therapeutic and spontaneous abortions reached the same conclusion. They also condemn therapeutic abortion from another viewpoint because of the fact that 80 per cent of tuberculous pregnant women deliver a perfectly normal child.

The main dictum in the care of tuberculous pregnant women is "treat the tuberculosis and disregard the pregnancy." Close cooperation between the obstetrician and the phthisiologist is an absolute requisite for a successful outcome. In active cases a strict sanatorium regime with absolute bed rest is essential as soon as the pregnancy is discovered. In those cases where tuberculosis develops after pregnancy has occurred, the sooner the lesion is discovered the sooner rational therapy can be

TABLE II. CASES OF INACTIVE TUBERCULOSIS

CASE	AGE	PARITY	TYPE OF DELIVERY	HOURS IN LABOR	KNOWN DURATION TB. PROCESS AT TERM	POST-PARTUM COURSE	FOLLOW-UP
1	35	ii	Spont. L.O.A.	5	1 year	Normal	Living and well
2	26	ii	Spont. L.O.A.	7½	3 years	Normal	Living and well
3	27	i	Spont. R.O.A.	8	2 months	Normal	Living and well
4	24	ii	Spont. L.O.A.	7½	3 years	Normal	Unknown

Analysis of Tables I and II reveals that of the 11 active cases there were 7 patients who died within three months of delivery and which can reasonably be considered post-partum deaths, giving an immediate mortality rate of 64 per cent for the active cases, and a mortality for the entire series of 47 per cent including those cases where follow-up could not be obtained. Among the active cases there was one death two years post partum. There was apparently no ill effect in the cases of inactive tuberculosis.

Parity apparently had no influence, there being 6 primiparas and 9 multiparas; although one would expect to find a greater mortality among the multiparas due to the added strain of successive labors and the additional care of one or more children. The average age in this series was twenty-eight.

There was no evidence of any interference with labor itself. There were 12 spontaneous deliveries and 3 patients delivered by prophylactic low forceps. The average duration of labor in the primipara was nine and one-half hours, in the multipara six and one-half hours.

There are several very significant and somewhat astounding facts noted in this series. In 10 cases, or 66⅔ per cent, the onset of tuberculous symptoms began after pregnancy occurred and in 8 cases, or 53 per cent, the tuberculous process was not discovered until the onset of labor. None of the active cases received sanatorium care or any adequate treatment during the course of their pregnancy. At first glance this would seem to be a serious indictment against the type of prenatal care given these patients, but it may be that this is but another proof of the insidiousness of the tuberculous process and the manner in which pregnancy brings to the fore a latent pulmonic lesion.

A review of the literature reveals that little is known of the true incidence of pulmonary tuberculosis in pregnancy, and a perusal of vital statistics from the Department of Health of the City of New York sheds no further light. However, available figures tend to show that pulmonary tuberculosis is no more likely to occur in pregnant than in nonpregnant women.

There have been several schools of thought concerning the true effect of pregnancy on pulmonary tuberculosis. The early investigators¹ of this subject held that pregnancy exerted a favorable influence on its course. Later, the pendulum swung to the opposite direction and the opinion was well nigh unanimous that pregnancy was fraught with great danger to tuberculous women. In recent years, however, there have been several articles purporting to show that pregnancy has no effect on pulmonary tuberculosis.

Thus, Barnes and Barnes² in a study of 535 sanatorium cases concluded that pregnancy does not necessarily exert a deleterious effect on pulmonary tuberculosis. Similarly, Hill,³ and Jennings and others,^{4, 5} in their statistical studies reached the same conclusion. Ornstein and Kovnat⁶ in reporting a series of 85 cases from the Sea View Hospital state that pregnant women with tuberculosis fare as well as their nonpregnant tuberculous sisters. On the other hand, Matthews and Bryant⁷ in their

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A STUDY OF 738 CASES OF UTERINE BLEEDING IN CONDITIONS OTHER THAN PREGNANCY

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IN A series of 4,421 admissions on the gynecologic service of a general hospital between 1928 and 1936 inclusive, abnormal uterine bleeding in conditions unrelated to pregnancy was observed or complained of as a symptom in 738 cases (16.6 per cent). The existence of pregnancy, intra- or extrauterine, automatically eliminated the case from this study, though the bleeding may have been due to factors unconnected with the pregnancy. It is manifest that in any large series the cases do not always categorically group themselves under one or another single etiologic heading. Associated conditions are frequently present in addition to the major lesion. In classifying such associated lesions the major pathologic condition, the one which was obviously or probably responsible for most or all of the bleeding, determined our choice of heading.

FIBROMYOMA

Fibromyoma occurred in 340 cases, or 46 per cent of the series. As is seen from Table I, the greatest number of these cases were treated by supravaginal hysterectomy, a procedure which yielded a mortality rate of 2.6 per cent. In the course of most of these operations the ovaries were removed if the patient was in the menopausal or premenopausal age. As Table I indicates, the series treated by curettage and radium was smaller but there was no fatality. The indications and contraindications of surgical and radiotherapy need not be reviewed here. This fact, however, impressed us forcibly, viz., that the simplicity of administration, the wider margin of safety, and economy in time and money strongly favor the use of radium. Both hysterectomy and radium find their greatest field of usefulness about and after the menopause. The results with radium in properly chosen cases are good, objectively and subjectively. Its use should always be preceded

instituted. For this reason the prenatal care in all pregnancies should include a careful chest examination and thorough investigation of any chest symptoms which may arise during the pregnancy.

Of late years, a powerful weapon has been added to the armamentarium in the battle against pulmonary tuberculosis, namely collapse therapy, especially artificial pneumothorax. Pneumothorax has been found to be especially fitted for use in pregnant tuberculous women and to give very gratifying results. However, it must at all times be remembered that pneumothorax is intended primarily to supplement sanatorium and bed rest therapy and not to replace them.

Such treatment should be continued until the onset of labor. Here every effort should be made to conserve the patient's strength and to minimize blood loss, trauma, and the chances of infection. With this in mind, certain clinics elect to perform a cesarean section. However, the shock of such a formidable procedure may result in a spread of the tuberculous lesion. The procedure of choice in conservative hands is the liberal use of sedatives to produce obstetric analgesia in the first stage of labor and as soon as the cervix is fully dilated, the application of forceps under local anesthesia, nitrous oxide or ethylene. Labor is made as easy and as short as possible. Obstetric complications are, of course, dealt with in the usual manner.

The patient having delivered, strict attention is again focused on the tuberculosis and the obstetrician and phthisiologist continue their close cooperation. The same regime is reinstituted as during the ante-partum period, and the use of pneumothorax is again brought into play. The mother is not allowed to nurse, since this has been found quite detrimental in pulmonary tuberculosis. Intensive treatment is continued until well past the puerperium when the case is turned over exclusively to the phthisiologist and further therapy is instituted as indicated.

CONCLUSIONS

1. Pregnancy has a definitely deleterious effect on active cases of pulmonary tuberculosis, especially in those cases in which the tuberculosis develops after pregnancy has occurred.
2. Careful attention should be paid to chest signs and symptoms during prenatal care.
3. In all cases of tuberculosis during pregnancy the patient should have strict sanatorium care and the use of artificial pneumothorax where indicated, plus the close cooperation of the obstetrician and the phthisiologist.
4. Delivery should be effected with a minimum of strain to the patient.
5. As a result of the modern conservative treatment of pregnant tuberculous women, the prognosis of this condition has definitely improved.

I wish to express my thanks to Dr. Charles A. Gordon whose kindly advice and many suggestions have made this paper possible.

that of one who has been deprived of her uterus, ovaries, or both; and this, irrespective of whether she bears children or not. It follows, therefore, that much can be achieved in the way of conservation of structure in cases which at first glance appear insuperable.

ENDOMETRIAL HYPERPLASIA

Next in frequency to fibromyoma in this series as the cause of bleeding was endometrial hyperplasia which was the only discoverable abnormality in 175 cases out of a total of 738 cases, or 23.7 per cent, approximately half the incidence of fibromyoma. In each case the diagnosis was made by the pathologist after careful microscopic examination.

The treatment most commonly employed was simple curettage which yielded satisfactory results, particularly in the younger age group. In patients who were at or about the menopause, the curettement was supplemented by radium. Radium was not employed in younger subjects unless one or more previous curettages and an adequate trial of endocrine therapy had failed to check the hemorrhage. When used before the premenopause the dose was between 400 and 600 mc. hr.

In those cases of endometrial hyperplasia in which an associated condition requiring laparotomy existed, follicular cysts of the ovaries were uniformly found, a finding which accounts not only for the hyperplastic condition of the endometrium consequent upon persistent ovarian stimulation but for the excellent results achieved by radiotherapy. It appears, therefore, that in uncomplicated endometrial hyperplasia, hysterectomy is contraindicated.

The small number of cases (9 in 175) in which hysterectomy was done, were at or after the menopause. The indications were associated pathologic lesions or failure to respond to less radical treatment.

There was one death in this group following a curettage and excision of a cervical polyp. This occurred in a patient seventy-one years of age who had diabetes. Death occurred seventeen days postoperatively from myocardial failure.

TABLE II. METHODS OF TREATMENT AND RESULTS IN ENDOMETRIAL HYPERPLASIA

OPERATION	CASES	RE- COVERED	IM- PROVED	UNIM- PROVED	DEATHS
Curettage	102	76	25	0	1 (0.9%)
Curettage and radium	64	44	19	1	0
Supravaginal hysterectomy	8	7	1	0	0
Vaginal hysterectomy	1	1	0	0	0
Total	175	128 (73.1%)	45 (25.7%)	1 (0.57%)	1 (0.57%)

FIBROSIS UTERI

Next in frequency to endometrial hyperplasia as a cause of bleeding was fibrosis uteri which occurred in 68 of the 738 cases, or 9.2 per cent. In those patients in whom hysterectomy was done, the diagnosis

by curettage and the curettings should be routinely subjected to microscopic examination. Occasionally, malignancy will be thereby disclosed where hitherto unsuspected, as occurred three times in this series. Despite the fact that in this series supravaginal hysterectomy was the procedure most commonly used, analysis of the results and the considerations beforementioned lead one to believe that radium will narrow the field of major surgery in the treatment of the fibroid uterus. Its advantages do not appear to be generally appreciated.

TABLE I. METHODS OF TREATMENT AND RESULTS IN FIBROMYOMA

OPERATION	CASES	RE- COVERED	IM- PROVED	UNIM- PROVED	DEATHS
Curettage	23	7	16	0	0
Curettage and radium	27	8	19	0	0
Supravaginal hysterectomy	192	174	12	1	5 (2.6%)
Total hysterectomy	8	7	0	0	1 (12.5%)
Vaginal hysterectomy	12	12	0	0	0
Laparomyomectomy	75	69	4	0	2 (2.6%)
Vaginomyomectomy	3	3	0	0	0
Total	340	280 (82.3%)	51 (15%)	1 (0.39%)	8 (2.3%)

It is not, in our opinion, sufficiently employed in cases where no contraindication to its use exists. Fibromyomas larger than a 3½ months gravid uterus and those complicated by degenerative changes within the growths or pelvic inflammatory disease were considered unsuitable for radium therapy. It is recommended that, before hysterectomy is resorted to for fibromyoma, a contraindication to the use of radium in a given case be established. In the menopausal cases 1,500 mc. hr. of radium were given, thereby establishing a permanent amenorrhea. The symptoms of the artificial menopause thus induced have been no more disturbing than in the natural climacteric. A survey of the causes of death following hysterectomy for fibromyoma indicates that myocardial failure occurred in 2 patients, pneumonia in 2, pulmonary embolus in 1, and paralytic ileus in 1. There were no deaths in the patients treated with radium.

During the childbearing age myomectomy was the procedure of choice, reaching the peak in the third decade; hysterectomy was most frequently done about the middle of the fourth decade; and radium enjoyed its greatest use several years later in the same decade. In a few instances, though over 20 fibroids had been enucleated it was possible to reconstruct a functioning uterus with a subsequent menstrual cycle. In one of these instances the patient's decision as to whether or not to consummate marriage to her betrothed entirely depended on the possibility of conserving her uterus. Twenty-three fibroids were enucleated, the uterus was reconstructed, and marriage ensued. As she has been practicing contraception for the past three years, it is not possible to submit an opinion as to her fertility. One may be assured, however, that the psychic state of a patient who knows by her catamenia that she has not been unsexed is much healthier than

immunity existed. It is believed, however, that the series is too small to be conclusive in the latter respect.

The 28 cases of malignancy, according to decade incidence, were distributed as follows: 14 in fourth decade; 9 in fifth; 4 in third; and 1 in sixth decade.

OTHER CONDITIONS

Polyps occurred in 49 cases (6.6 per cent) of which 43 (5.8 per cent) were cervical and 6 were uterine (0.8 per cent). No instance of malignancy in a polyp was observed.

Chronic inflammatory disease as a cause of bleeding was noted in 24 cases (3.2 per cent). The bleeding, as a rule, was not the most prominent symptom in this group. Conservation of genital structure and function was held paramount in the treatment of the younger patients in whom, in fact, this lesion most frequently was observed.

Benign ovarian neoplasms occurred in 18 cases (2.4 per cent) of which 13 were cysts, 4 fibromas, and one a granulosa cyst.

Anatomic displacements as causes of bleeding were found in 29 patients (3.9 per cent). They responded well to plastic operations which reduced or eliminated tissue drag and circulatory embarrassment involving the ovary. In younger women preservation of the reproductive function, here as elsewhere, determined the choice of operative procedure. Retroversion in this class of patient was corrected by a round ligament operation after the method of Olshausen or Gilliam. When childbearing was no longer a factor, the Watkins interposition operation and tubal sterilization have proved satisfactory. Very rarely were vesical symptoms pronounced enough to militate against the value of the procedure. In recent years the Fothergill operation has been coming into increasing vogue. The results have been good.

There was one case of fibrosis of cervix and 2 of glandular hyperplasia of cervix in all of which the bleeding was not marked. Finally, there were 4 patients in the series in whom no lesion within or without the uterus could be found to account for the bleeding. Blood dyscrasia was ruled out. These cases were classified as of undetermined cause, probably endocrinopathic.

SUMMARY

1. In a series of 4,421 admissions on the gynecologic service of a general hospital, abnormal uterine bleeding due to conditions unrelated to pregnancy was present in 738 patients (16.6 per cent).

2. The commonest single cause of bleeding in the 738 cases was fibromyoma which occurred in 340 (46 per cent). Though supravaginal hysterectomy was the procedure most commonly employed, the impression gained has been that radium insertion on account of its safety, efficiency, technical simplicity and economy of time and money will narrow the field of major surgery in the treatment of the

of "fibrosis" was made by the pathologist. In the other patients the diagnosis was made clinically by the presence of a uniformly enlarged, hard uterus in a subject generally about the menopause who suffered from meno- or metrorrhagia.

The method of treatment employed in young women (i.e., those in whom future childbearing is a factor) was simple curettage. If the bleeding recurred within a period of one to several years the curettage was repeated one or more times. Radium, even in small doses (400 to 600 mc. hr.), was used infrequently and reluctantly during the childbearing age, and only in patients who failed to respond to prolonged endocrine therapy and repeated curettage, and in whom the bleeding was severe enough to affect the general health. A castration dose was never given before the premenopause.

The most suitable patients for radium were those in the menopausal age. The symptoms of the artificial menopause thus induced were, as in the fibromyoma group, no more pronounced than in the natural change, while relief from anxiety over pregnancy (imaginary or otherwise) improved the psychic status appreciably. The results were good. Hysterectomy was less often resorted to in the menopausal group than radium. There were no deaths in the radium treated series as compared with one death in the hysterectomized group. It appears, therefore, that hysterectomy should be given second consideration in the treatment of this condition, and used only after radium has failed to control the bleeding unless there is associated pathology which requires laparotomy.

TABLE III. METHODS OF TREATMENT AND RESULTS IN FIBROSIS UTERI

OPERATION	CASES	RE- COVERED	IM- PROVED	UNIM- PROVED	DEATHS
Curettage	12	5	7	0	0
Curettage and radium	34	21	13	0	0
Supravaginal hysterectomy	19	15	3	0	1 (5.2%)
Vaginal hysterectomy	2	2	0	0	0
Total hysterectomy	1	1	0	0	0
Total	68	44 (64.7%)	23 (33.7%)	0	1 (1.45%)

MALIGNANT NEOPLASMS

The total number of malignant neoplasms was 28 in a total of 738 cases, or 3.7 per cent. There were 12 cases of carcinoma of cervix; 9 of carcinoma of corpus; 3 of sarcoma of corpus; 2 of carcinoma of ovary; 1 of sarcoma in fibroid; and 1 of granulosa cell tumor of ovary. The frequently observed lower incidence of carcinoma of the cervix in Jewish women is evident in this series. Although over 90 per cent of the patients in the entire series were Jewish, it was observed that the 12 cases of carcinoma of the cervix were equally distributed between Jewish and non-Jewish patients. Analysis showed that in the case of malignant neoplasms of the corpus and ovary no such relative racial

HYPERPYREXIA PRODUCED BY THE HOT BOX IN COMBINATION WITH THE ELLIOTT TREATMENT

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THE history of the beneficial effects of artificial fever in the treatment of gonorrhea is now well known due to the numerous papers published on this subject in the last five years. Hyperpyrexia is no doubt a major step forward in the care of this disease particularly in the female and even more especially when arthritis is associated with it. In the latter instance, it may perform miracles.

However, the treatment as originally performed by Carpenter and Warren¹ may be dangerous and can be trusted only in the hands of a few highly specialized workers. It requires the constant attendance of a physician and even in his presence, heat strokes and unavoidable sequelae may occur. This refers to the type of treatment in which a fever of 106.7° F. by rectum for periods of five to twenty hours or multiple treatments of shorter periods is induced by radiant heat in an enclosed space or hot box. In these cases restraints are necessary and the pulse rate reaches 160; the patient is frequently on the brink of a heat stroke and collapse. Experience with this method makes one conclude that it is far more dangerous than the disease.

Bishop, Lehman, and Warren² in their paper of a comparison of 3 electrical methods of producing hyperthermia show two charts with pulse rates continually ranging between 170 and 190 beats per minute at a temperature of 106.7° F. These authors have treated 111 patients, 64 females and 54 males, the single hyperpyrexia lasting from five to seventeen hours though less than the thermal death time of the organism with 80 per cent of them cured. A later report of 100 cases treated at the thermal death time gave 87 per cent cures and 1 death is reported. Desjardins, Stuhler and Popp³ cured 40 out of 45 patients by 2 to 4 treatments of five or six hours each. Bennett and Austin⁴ treated 16 patients in a similar manner and obtained 12 cures. Anderson, Arnold and Troutman⁵ cured 39 of 54 patients by this method, all the patients being males. It would appear from these reports that the treatment is efficacious and without particular danger.

In order to lower the pulse rate Simpson, Kislig and Littler⁶ were the first to appreciate the value of air conditioning the hot box, as the greater the saturation of the air with moisture, the less perspiration is evaporated on the skin surface, and therefore the less the cooling effect. Their results are the same as others though the patients are more comfortable. However, they report minor burns (vesicles) in about 3 per cent of the cases.

The "hot box" was used for one year at Bellevue Hospital following the original technique of Carpenter and Warren¹ and in spite of constant medical aid, we had three major calamities. One patient died from heat stroke and two others had severe heat strokes with resulting deep burns that necessitated skin grafting and long hospitalization netted only 55 per cent cures. Aside from the serious and fatal complications of this type of treatment, the discomfort to the remaining cases was so great that few patients would submit to more than one

fibroid uterus. Fibroids larger than a 3 and one-half months gravid uterus and those undergoing degenerative changes or complicated by pelvic inflammatory disease are not suitable for radiation.

3. Myomectomy, single or multiple, is the procedure of choice in younger women.

4. Next in frequency to fibromyoma as the cause of bleeding was endometrial hyperplasia which occurred in 175 patients (23.7 per cent). Simple curettage in younger subjects yielded good results in the vast majority of patients while curettage with radium insertion in the menopausal group yielded excellent results. Whenever laparotomy was performed for some complicating condition, follicular cysts of the ovary were observed in association with endometrial hyperplasia.

5. Next in frequency was fibrosis uteri which occurred in 68 patients (9.2 per cent). The best results were achieved in the menopausal group in which the treatment par excellence is curettage and 1,500 mc. hr. of radiation with the element inserted in the fundal area of the uterus. It is believed that hysterectomy should not be performed except in those rare instances in which radium has failed.

6. There was no fatality following the use of radium in fibromyoma, endometrial hyperplasia and fibrosis. With hysterectomy, the results were less favorable.

7. The total number of malignant neoplasms of the reproductive organs was 28 (3.7 per cent). A relative immunity to carcinoma of the cervix was noted in Jewish patients. No such immunity was evident with respect to malignant neoplasms of the corpus and ovary.

8. No instance of malignancy was observed in 49 polyps (6.6 per cent) of which 43 were cervical and 6 uterine.

Grateful acknowledgement is due to Dr. Leo Schwartz, Chief of Staff, for his cooperation in this survey as well as to the various staff members whose case records have been utilized. For the arduous task of arranging preliminary data credit is due to Messrs. H. Merenstein and H. Levy.

4506 TWELFTH AVENUE

Lash, A. F.: Surgical Treatment of Puerperal Sepsis, *Am. J. Surg.* 37: 68, 1937.

Surgical treatment should be utilized in certain types of puerperal sepsis in conjunction with medical treatment. These surgical cases can be determined by history, repeated examination and thorough and constant clinical study.

The operations employed by Lash were colpotomy, abdominal drainage and removal of diseased structures and hysterectomy, each operation being employed in certain pathologic states. Vein ligation has been done so rarely in the Cook County Hospital and the mortality in these patients is so low that the tendency now is entirely toward conservative management with repeated blood transfusions.

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rectal temperature is taken every twenty minutes, and if it is more than 2.5° F. higher than the mouth temperature, the latter is very carefully rechecked. No alarm is felt for the condition of the patient unless the pulse is around 150 with a dropping blood pressure. She is given only water and orange juice to drink during this treatment. After six hours of maintained temperature of 105° F., the box is opened and the patient put to bed. It is important to check the temperature every twenty minutes for two hours after the treatment to make sure the temperature has dropped to normal, as heat stroke can occur after the cessation of the treatment.

Seventy-nine patients treated by the combination of hot box and Elliott treatment had a total of 148 treatments without any major complication. One patient showed impending symptoms of heat stroke one and one-half hours after the start of the treatment when her temperature was only 104° F. She gave a past history of encephalitis which undoubtedly made her heat sensitive. The treatment was stopped and she was never in danger, yet developed a mild burn in that short period of time. The treatment was stopped in 2 other instances because of the rate of pulse. No damage resulted, but these partially treated cases are included as failures.

Occasionally some patients will develop small blisters, especially about the lower abdomen and hips, but these are of no importance and do not occur if covered with a blanket. It is not uncommon to find blistering of the vagina from the Elliott bag, but this condition heals readily and never causes scars or strictures.

Of the 79 patients treated, 23 had only one treatment with 15 cures, while 50 patients had 2 treatments with 42 cures (84 per cent cured). Of 5 patients submitted to a third treatment 2 were cured. Only 1 patient had a fourth treatment and this resulted in a cure.

With one treatment, 15 patients were cured out of 23, showing that the thermal death time of the organisms not killed was over six hours at this particular height of temperature. Most of these patients refused to repeat the treatment or left the hospital. Even some failures, however, benefited to a certain extent, for 3 had negative cervical and 3 negative urethral spreads.

Forty-two out of 50 were cured by two treatments. Two of the failures occurred at the beginning of the series and were not carried out at maximum temperature and the entire second treatment was not completed, while the remaining failures can only be explained on their heat resistancy. This same explanation can account for the 60 per cent failures of the 3 treatment series, as demonstrated by the Rochester group of workers, Boak, Carpenter, Mucci and Warren^{7, 8} who have determined the in vitro thermal death time of 250 strains of gonococci and found this to vary between six and 34 hours at 106.7° F.

Sixteen of the 50 patients receiving treatment had arthritis and were uniformly benefited, being listed on discharge as 90 per cent to 95 per cent improved. Eight received one treatment and 8 two treatments. None of these cases were transferred to a hospital for chronic diseases. This was frequently a necessity in the past because of their necessarily long hospitalization.

Two cases of gonorrhea complicated by early pregnancy, have been treated by this method, both requiring 3 treatments. Neither one aborted and one was cured, the other showing a positive urethra but a negative cervix after treatments.

Short wave therapy was substituted for the Elliott treatment in another series of cases in the hope that we could get a still higher pelvic temperature while maintaining the same mouth temperature. Using the short wave machine with a vaginal diathermy applicator at a temperature of 108° F., and the indifferent pad on the abdomen, we did obtain higher rectal readings and should therefore have expected better results.

The patients are just as comfortable with this form of therapy but sweating in the presence of the electric current keeps the nurse on the alert to prevent burns. These burns occur wherever the wires, pad, or vaginal pole touches the patient. In this series we have had three patients who developed pain and swelling on the

treatment. Meanwhile, reports from other clinics stated that 4 to 6 treatments were not unusual for a cure, and it was felt that our failure to employ multiple treatments accounted for the low percentage of cures, namely 55 per cent.

Notwithstanding these poor results, it was believed that heat was the proper means with which to attack gonorrhea, and an attempt was made to perfect a technique which would eliminate the generalized dangers and discomforts and which still could be carried out in a simple fashion.

Such a treatment would seem to require a prolonged high pelvic temperature to kill the gonococci and a lower cerebral temperature, which would not kill or endanger the life of the patient. The higher the cerebral temperature the more symptoms of medullary stimulation will be exhibited by the patient—fast pulse, rapid respiration, vomiting and restlessness—and thus the patient comes nearer to a heat stroke and collapse. The lower the cerebral temperature the greater became the margin of safety and the greater the general comfort of the patient.

To obtain this happy medium, a regular hot box treatment was given, but the mouth temperature was maintained at 105° F., and at the same time a continuous Elliott treatment was carried out with the water in the vaginal bag at 115° F. The resultant temperature curves show the rectal temperature to be 2° to 2.5° F. higher than the mouth temperature during the treatment. By this method the rectal temperature is higher than the 106.7° F. induced by radiant heat alone in the discarded type of fever therapy; the general condition of the patients is never a cause for alarm after the first hour, when they exhibit slight restlessness. The pulse stays around 140 or lower; no restraints or heavy sedatives are necessary. The patient is under the constant care of a nurse trained in this work, and she calls for a staff doctor if any unusual symptoms occur. The former treatment necessitated the constant attendance of a physician; the present treatment requires his presence only until the fever reaches a maximum.

PROCEDURE

The technique is simple and suitable for the average hospital staff, not necessitating a special training in physiotherapy. The only contraindications to the treatments are: (1) Those patients who are running a temperature of 102° F. or over from salpingitis or other causes. One may except from this, patients with gonorrheal arthritis or septicemia. These patients should be treated as soon as possible. (2) Intact hymen, as it will not allow insertion of the vaginal bag. (3) General medical contraindications as heart disease, tuberculosis, etc.

The patient is given 3 gr. of sodium amytal the night before the treatment and an enema the following morning. When she is put in the hot box the body is covered with a blanket to increase the humidity around the skin surface and to prevent burns. The Elliott vaginal bag is inserted in the vagina and the cork is wound with cotton padding. The Elliott machine is set for 115° F. and runs automatically. Occasionally its temperature will go over 115° F. and must be lowered with ice water. The doors of the hot box are closed and the bulbs are turned on full. When the temperature reaches around 103° F. the patient becomes restless and $\frac{1}{6}$ of a gr. of morphine sulphate and $\frac{1}{200}$ of a gr. of scopolamine is administered by hypodermic. This is repeated in three or four hours. The mouth temperature is taken every ten minutes. Cold fluids should not be given just preceding this. The nurse holds the lips shut over the thermometer as the patient is usually drowsy. The

HYPEREMESIS GRAVIDARUM

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IT IS generally stated that approximately one-half of all pregnant women have some degree of nausea and vomiting in the early months of pregnancy. In rare instances the vomiting becomes more frequent and severe.

A study concerning the cases admitted to the University Hospital for hyperemesis gravidarum may be of interest. From June, 1921 to January, 1937, there were 87 patients admitted with this diagnosis. Table I shows that the greatest percentage of cases in the entire group of white and colored occurred between 21 and 25 years of age. This is especially true for the white patients, but it is interesting to note that the greatest percentage of cases among colored patients occurred at an earlier age, probably because these individuals begin their childbearing career younger.

TABLE I. AGE INCIDENCE

	TOTAL	PER CENT	WHITE	PER CENT	COLORED	PER CENT
18-20	16	18.4	10	14.5	6	33.3
21-25	27	31	25	36.2	2	11.1
26-30	16	18.4	11	15.9	5	27.8
31-35	22	25.3	18	26.1	4	2.2
36-40	6	6.9	5	7.2	1	5.6

Table II shows that 95.4 per cent of all the cases occurred in married women and that slightly over one-fourth of the cases occurred among primiparas.

TABLE II. MARITAL STATUS AND GRAVIDITY

	TOTAL	PER CENT	WHITE	PER CENT	COLORED	PER CENT
Married	83	95.4	68	98.6	15	83.3
Single	4	4.6	1	1.4	3	16.7
Primipara	24	27.6	18	26.1	6	33.3
Multipara	63	72.4	51	73.9	12	66.7

Table III refers to the duration of pregnancy on admission to the hospital. It will be seen that the majority of the cases occurred prior to the twelfth week. The correctness of the diagnosis in some of the cases which occurred late in pregnancy may be questioned, as a careful review of the histories points strongly to pyelitis as an etiologic factor in at least two of these.

TABLE III. DURATION OF PREGNANCY

WEEKS	TOTAL	PER CENT	WHITE	PER CENT	COLORED	PER CENT
4-8	18	20.7	13	18.8	5	27.8
8-12	50	57.5	42	60.8	8	44.4
12-16	10	11.5	8	11.6	2	11.1
16-20	1	1.1	1	1.4	0	0
20-40	8	9.2	5	7.2	3	16.7

inner aspect of the thigh where the wire from the vaginal pole touched them causing a condition resembling a high femoral phlebitis. However, no ill effects resulted, nor did the skin slough.

Vaginal blisters occur with the same frequency as with the Elliott treatment but instead of healing they have a tendency to penetrate to a greater depth. In this small series, two patients developed vesicovaginal fistulas which had to be repaired by surgery. Scar tissue about the opening made these more difficult to repair than the usual fistula of traumatic origin.

In this series of 14 patients, 4 received 1 treatment and 3 were cured and 7 patients received 2 treatments with 5 cures. Three patients were treated with both types of combined methods and 2 were cured. These results are good, but the character and incidence of complications compelled us to abandon the short wave machine.

CONCLUSIONS

1. Hyperpyrexia sustained in the hot box alone at the temperature of 106.7° F. is a very drastic and heroic treatment for the cure of gonorrhea in the female. It requires constant medical supervision in spite of which heat stroke and serious burns may occur.

2. Hyperpyrexia sustained in the hot box in combination with the pelvic short wave therapy, while safe from heat stroke, may produce burns some of which result in the production of vesicovaginal fistulas.

3. Hyperpyrexia sustained in the "hot box" in combination with the Elliott Treatment gives good results without generalized or local dangers. This treatment, therefore, does not require the continual attention of an expert physiotherapist and can be entrusted to a trained nurse. It is adaptable to the average hospital staff. Two treatments with an interval of two days' rest will result in cure in about 84 per cent of cases of acute gonorrhea.

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tering the hospital, her temperature was 100.6° F., pulse rate 140, albumin, acetone and diacetic acid were found in the urine, and hemorrhages were present in both fundi. Her pregnancy was interrupted and she made an uneventful recovery. The other white patient was a thirty-five-year-old multigravida about twenty weeks pregnant who had been vomiting a number of weeks prior to admission to the hospital. Her temperature was 98.6° F., pulse rate 100, with only a slight trace of albumin in the urine. Examination of the eye grounds showed hemorrhages in both fundi, but since this case occurred several years ago the patient was treated conservatively, and showed immediate response to the type of therapy employed and was discharged from the hospital in good condition without an interruption of her pregnancy. The third case occurred in a colored multigravida, aged eighteen years, who was admitted to the hospital in her twelfth week of pregnancy after about six weeks of vomiting at home. On admission, her temperature was 102° F., pulse rate 120, and albumin, acetone, and diacetic acid were present in the urine. She showed hemorrhages and exudate in both fundi. In spite of the interruption of the pregnancy, this patient died. It is quite possible that an earlier interruption of pregnancy might have resulted differently.

TABLE VI. TREATMENT

	TOTAL	PER CENT	PER CENT	WHITE	COLORED	PER CENT
Treated conservatively	70	80.5	59	85.5	11	61.1
Interrupted	17	19.5	12	17.4	5	27.8
Hemorrhages in eye grounds	3	3.4	2	2.9	1	5.6
Eye grounds normal	32	36.8	26	37.7	6	33.3

So far as the results are concerned in this series of patients, 89.7 per cent of the entire group may be classified as good, the frequency of a good result being 92.8 per cent among the white patients and 77.8 per cent among the colored. Four patients, or 4.6 per cent, were discharged from the hospital unimproved. In every instance there was a marked lack of cooperation on the part of the patient, necessitating her discharge from the hospital against the advice of the attending physician. Five patients died, a percentage of 5.6 for the entire series. Two of these were white patients, and 3 colored, giving percentages of 2.9 and 16.7, respectively. Several points are brought out by these figures, such as the often questioned occurrence of so-called neurotic vomiting among colored patients which can be cured without an interruption of the pregnancy. It is also clear, however, that there is a markedly increased mortality

TABLE VII

	TOTAL	PER CENT	WHITE	PER CENT	COLORED	PER CENT
Good	78	89.7	64	92.8	14	77.8
Unimproved	4	4.6	3	4.3	1	5.6
Died	5	5.6	2	2.9	3	16.7
Autopsy	2	40				
Days of hospitalization	1,013	12.8*	706	10.2*	307	17*

*Days per patient.

Table IV on the duration of vomiting prior to hospitalization brings to light many cases in which the vomiting had continued for a considerable length of time before proper treatment was instituted. As a result of this, many patients were admitted in relatively poor condition, showing the effects of starvation.

TABLE IV. DURATION OF VOMITING

WEEKS	TOTAL	PER CENT	WHITE	PER CENT	COLORED	PER CENT
Less than 1	1	1.1	1	1.4	0	0
1-2	10	11.5	6	8.7	4	2.2
2-4	46	52.9	37	55.2	9	50.0
4-8	22	25.3	20	29.0	2	11.1
8-16	8	9.2	5	7.2	3	16.7

Table V shows that more than one-third of the patients suffered from nausea and vomiting in previous pregnancies, and that two patients of the entire series had therapeutic abortions performed for hyperemesis gravidarum in a previous pregnancy. The frequency of syphilis in this group of cases does not show any particular relationship between this disease and hyperemesis. It is clearly demonstrated in the cases under consideration, pregnancy being interrupted 17 times, that any or all of the items just mentioned are by no means incompatible with a continuation of the pregnancy, provided that the patient is properly treated.

TABLE V. ASSOCIATED FINDINGS

	TOTAL	PER CENT	WHITE	PER CENT	COLORED	PER CENT
Nausea and vomiting in previous pregnancies	33	37.9	27	39.1	6	33.3
Therapeutic abortion for vomiting in previous preg.	2	2.3	2	2.9	0	0
Positive Wassermann	4	4.6	1	1.4	3	16.7
Temperature over 99° F.	43	49.4				
Pulse over 100	25	28.7				
Albuminuria	27	31.0				
Acetonuria	59	67.8				
Diabetic acid	41	47.1				

In this series 70 patients were given so-called conservative treatment, consisting of glucose, sedation and complete isolation in addition to a period of from twenty-four to forty-eight hours of starvation. Seventeen of the pregnancies were interrupted or 19.5 per cent of the entire group. Twelve interruptions of pregnancy were done among the white patients, and 5 among the colored; giving an incidence of 17.4 per cent and 27.8 per cent, respectively, for the two races. In addition, Table VI shows that the eye grounds were examined in only 35 cases, all of these being in more recent years since our attention has been called to the significance of eye ground changes in this disease. Hemorrhages in the eye grounds were found in 3 cases, this complication occurring twice among the white patients, and once among the colored. One of these patients was a white primigravida, aged 14 years, who had been vomiting for five weeks prior to admission to the hospital and who at the time of admission was approximately fourteen weeks pregnant. On en-

Corroboration was given in papers by Schmidt,⁹ Voncken,¹⁰ Chase,¹¹ Tuthill,¹² Strauss,¹³ and Friedman,¹⁴ all of whom reported that spontaneous subarachnoid hemorrhage in young people in the great majority of instances is caused by a ruptured aneurysm of congenital origin.

Schmidt drew attention to the frequent difficulty of finding the aneurysm and emphasized that failure to find an aneurysm does not exclude its existence.

McIver and Wilson,¹⁵ and Stengel and Wolferth¹⁶ believe that mycotic emboli from diseased valves may produce inflammatory lesions of small cerebral blood vessels; and in this way weaken the wall of that vessel through a degenerative process, thus leading to mycotic aneurysm and hemorrhage. In Fearnside's collection of 44 cases of intracranial aneurysms, 13 were due to vegetative endocarditis and septic emboli.

Hypertensive disease or cerebral arteriosclerosis is the most common etiologic factor in aneurysmal formation in patients past middle life, although age does not rule out congenital origin.

Turnbull¹⁷ especially has proved that syphilis is an exceedingly rare cause of intracranial aneurysm; there were none in his and Fearnside's material of 44 cases.

In the absence of generalized disease many patients go through life without ever having symptoms pointing to an intracranial aneurysm, except chronically recurring headache. Bassoe¹⁸ in his treatise on migraine in relation to cerebral vascular lesions reported spontaneous subarachnoid hemorrhage to be relatively frequent in migraine patients. He suggests that the previous migraine-like headache may have been directly due to the congenital aneurysm, and was not true migraine. Goldflam,¹⁹ Adie,²⁰ Critchley and Ferguson,²¹ cite other cases in point, and advocate similar views.

Parker²² believes that the correct diagnosis of a cerebral aneurysm during the life of the patient has been regarded as somewhat difficult. It is only in the cases of cerebral aneurysms with intermittent leakage or rupture that correct diagnosis of the aneurysm is possible. Much more interesting clinically are the cases of intermittent leakage of blood from an aneurysmal sac with alternating episodes of disturbed function and periods of relatively poor health. This phenomenon occurred in 31.1 per cent of Wichern's cases, and in Fearnside's series of 44 cases it was present in about 42 per cent of his nonembolic aneurysms. In these cases there was a history of two, three or more episodes separated by varying intervals.

A thorough search of the literature revealed few published reports, indicating the rarity of recognized cases of spontaneous subarachnoid hemorrhage complicating pregnancy, labor, and the puerperium.

Russel²³ observed the disease in 5 cases, Masten²⁴ in 2 cases, Stroink²⁵ in 2 cases, Ohler²⁶ in 1 case, Strauss in 2 cases, and Smith²⁷ in 1 case. Of these 13 cases reported by the above authors, it is interesting to note that in 8 there was a definite association between this syndrome and toxemia of pregnancy. On the basis of this finding one may have to consider the question of toxemia as a possible cause of subarachnoid hemorrhage, since spontaneous subarachnoid bleeding may result from the bursting of a congenital aneurysm under the strain of hypertension.

Subarachnoid hemorrhage is a striking syndrome with sudden onset of severe headache, vomiting, stupor, or coma, depending upon the size of the rent in the vessels, and slow pulse. Either the patient succumbs immediately to a fulminating hemorrhage; or if she does not, there develops the secondary stage, a meningeal syndrome a few days later. During this stage one finds fever, pain, and rigidity of the neck and positive Kernig sign, and leucocytosis. The most significant of all the findings is the presence of blood in the cerebrospinal fluid under increased pressure. It may vary in color from a pink to a dark red or deep orange. It is intimately mixed with the fluid in the three tubes; it does not clot, and the supernatant fluid on standing is xanthochromic or yellow. In many cases, perhaps the majority, the prodromal symptoms are mild; the initial attack being followed by apparent recovery. Leakage or recurrence of bleeding may occur intermittently. Two to four episodes may occur prior to the final and fatal rupture.

rate among colored patients suffering from hyperemesis gravidarum. The advisability therefore of treating the condition more radically in colored patients seems to be well borne out. Table VII also shows an average hospital stay of 12.8 days per patient, the figure for the colored patients being considerably higher than that for the white.

SUMMARY

Hyperemesis gravidarum, while a fairly rare complication of pregnancy, does occur with sufficient frequency to create considerable interest. Although the neurotic element cannot be definitely proved, it does seem to play a rather important part in increasing the severity of the symptoms. General rules for treatment are impossible, it being necessary to individualize each case. Many patients will respond to conservative and suggestive therapy. A few require interruption of pregnancy, and in the latter group certain precautions are of the greatest importance.

MATERNAL INTRACRANIAL HEMORRHAGE COMPLICATING LABOR*

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WE WISH to present three cases of maternal intracranial hemorrhage complicating labor observed during the last four years at the Beth Israel Hospital.

Although spontaneous subarachnoid hemorrhage was noted by Bramwell¹ in his classic description of the disease in 1886, its symptomatology has been recognized only in recent years and differentiated from other forms of spontaneous intracranial hemorrhage.

Studies by Eppinger,² Wichern,³ Fearnside,⁴ Hassin,⁵ Symonds,⁶ and Sands⁷ have thrown considerable light on the subject and have established it as a definite clinical entity, one that lends itself to a correct diagnosis.

The occurrence of such hemorrhages in young persons has led many observers to assume that a congenital weakness or defect of the vessel wall leads to the aneurysmal deformity, which later under the strain of hypertension ruptures, causing bleeding.

Fearnside proved that congenital aneurysms must be of not infrequent occurrence, for they were found fifteen times in a series of 5,432 consecutive examinations of the head, one in every 362 cases.

In 1930 Forbes⁸ demonstrated that a number of hitherto unexplained intracranial hemorrhages in young persons can be accounted for on the basis of ruptured intracranial aneurysms of congenital origin in whom there is no evidence of syphilis or atheroma. He found 12 aneurysms in 70 routine necropsies. He called attention to frequent muscular defects in the media of cerebral arteries at the point of their bifurcation, or in the origin of a branch; usually situated on the circle of Willis, or the vessels in its immediate vicinity. This is significant, for it establishes the existence of weak points in a vessel wall, and thus serves as points of predilection for aneurysm. In none of the aneurysms studied in this series can muscle be demonstrated in the wall of the sac.

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after hardening. All the ventricles were moderately distended. A large intraventricular mass of clotted blood was found tightly filling the fourth ventricle, thus explaining the sudden death. The clot in the third ventricle appeared smaller. The major portion of the pons was occupied by irregular hemorrhage. No tumor and no aneurysm or varix could be discerned with the naked eye. Further slicing of the pontine hemorrhage revealed a still larger hemorrhage, which, in the part of the pons nearest the fourth ventricle, reached a transverse diameter of 3.5 cm. and a vertical one of 3 cm. At this level no brain tissue could be seen throughout the hemorrhage. The hemorrhage also encroached upon the lower leg of the right internal capsule. The region of the corpus of Luys was almost entirely destroyed by the hemorrhage. On a horizontal cut the continuity between the pontine hemorrhage and the clot in the fourth ventricle was seen.

Microscopic Examination: Sections from different areas of the brain did not show any hemorrhage or lesion of blood vessels.

Comment.—The case here reported of intracerebral hemorrhage is of unknown origin. No evidence of hypertensive disease, endocarditis, or congenital aneurysm could be found. The significant findings would indicate that this patient had numerous signs of an abnormal constitution; namely, obesity, late onset of menses, adenoma of hypophysis and abnormal nerve structure in the hypophysis, goiter, and splanchnomegaly. This may in a certain measure explain some abnormality in vessel structure which made the so-called spontaneous hemorrhage possible. It certainly is possible that there may have been an aneurysm in the pons which was destroyed by the hemorrhage beyond recognition and therefore escaped notice.

CASE 2.—R. A., para ii, gravida iii, aged 26 years, married, presented herself for prenatal care on Nov. 12, 1935. The family history was unimportant. She had had a renal calculus in her left kidney for which a pyelotomy and nephrotomy was done in March, 1935. The past history revealed the fact that for about three years she had been treated in various clinics for chronically recurring headaches, with no relief. The diagnosis could not be determined. Onset of menses began at 11 years, occurring every twenty-eight days, lasting three days. The last menstrual period was June 25, 1935, and the expected date of delivery was April 1, 1936. She had been delivered spontaneously at term, nine and seven years before. The babies weighed 5 pounds and 5 pounds 13 ounces, respectively. The puerperium was normal. The physical examination was negative. She weighed 125 pounds. The heart and lungs were normal. The blood pressure was 122/62. The urine showed a faint trace of albumin. Blood Wassermann was negative. The pelvic measurements were ample. Subsequent ante-partum examinations showed the blood pressure to range between 110/80 and 100/60. Urinalysis showed a faint trace of albumin. She had gained 21 pounds. Onset of labor occurred at term on March 28, 1936, at 12 noon.

On admission to the hospital at 4:30 P.M. the same day the head was engaged in L.O.A. position, and the cervix was two and one-half fingers dilated. The physical examination was negative. The heart and lungs were normal as were apparently the abdominal viscera. The blood pressure was 130/90. She delivered spontaneously at 6:05 P.M. The weight of the baby was 8 pounds 2 ounces. The total duration of labor was six hours and fifteen minutes. The patient received $\frac{1}{2}$ c.c. of pituitrin following the birth of the baby, and 1 c.c. of ergobasine subsequent to the delivery of the placenta.

At 8:15 P.M., two hours after delivery, the patient vomited and complained of severe headache, dizziness, pain in both eyes, and dimness of vision. There was no loss of consciousness or stupor. The skin was cold and clammy. Both hands were cyanotic up to the wrist. The blood pressure rose to 170/90. The pulse was 64. Ergotism was suspected. A catheterized specimen of urine was acid; specific gravity 1010, with a trace of albumin, no glucose or diacetic acid; microscopically, many red and white blood cells. A chemical examination of the blood showed the non-protein nitrogen to be normal.

The following morning, March 29, the blood pressure dropped to 105 systolic and 70 diastolic and remained constantly at this level. The hands felt warm and appeared entirely normal. A neurologic examination disclosed the following: The patient was in deep stupor but responded promptly and irritably to painful stimuli.

The syndrome of subarachnoid hemorrhage must be differentiated from intracerebral hemorrhage. It differs from the latter by the presence of pronounced meningeal signs, the frequent occurrence of papilledema and paralysis of the extrinsic ocular muscles, and the lack of focal signs.

REPORT OF CASES

CASE 1.—Y. A., para 0, gravida i, aged 25 years, married, presented herself for prenatal care on Aug. 8, 1933, in the fifth month of her pregnancy.

The family history was negative. The patient stated that she had had measles and scarlet fever as a child, but no serious illness or operation.

Her menstrual periods commenced at the age of 17 years and were irregular, occurring every thirty to thirty-five days, and lasting from two to three days. The flow was scant. The last menstrual period was March 23, 1933. The expected date of her confinement was Dec. 30, 1933.

Physical examination revealed a short, well-developed obese women, weighing 175 pounds. The heart and lungs were normal. Blood pressure was 108/68. Pulse 90. The urine, blood Wassermann, and pelvic measurements were normal. Subsequent antepartum examinations showed the blood pressure to average about 110/60; urinalyses were repeatedly negative. There were no complaints.

Following her last visit to the clinic on October 3, the patient failed to report again for eight weeks. After much persuasion she was induced to return and she presented herself at the clinic on December 12.

There seemed to be nothing unusual about her condition at this time, until she rose from her seat to walk across the room, when she suddenly became dizzy and pitched forward on her face. She did not faint, nor did she lose consciousness. She regained her composure very quickly. The blood pressure was 125/70 and the urine examination was negative. There was no edema of the face, body, or extremities, and no history of headache or visual disturbances. Nor was there any evidence of paralysis of any part of the body. The pupils reacted well. Further questioning at this time revealed the fact that on several occasions during the pregnant state between the period of October 3 and December 12, the patient was subject to frequent attacks of syncope.

Onset of labor occurred at term on Jan. 4, 1934, at 4:30 P.M. The patient was admitted to the hospital on Jan. 5, 1934, at 6:15 A.M., having good uterine contractions at seven-minute intervals. The temperature was 99.2° F., pulse 80, and respirations 20.

The general physical examination on admission was essentially negative. The blood pressure was 140/100. The urine was negative. Rectal examination disclosed the vertex to be engaged above the spines in an R.O.A. position; the cervix was two-plus fingers dilated and thick; the membranes were intact and the fetal heart was in good condition. Pains occurred every five minutes.

The patient had been perfectly well until 11:15 A.M., when she was seized with sudden severe headache and dizziness.

At 11:40 A.M. (twenty-five minutes after the onset of her initial complaint) she was stricken with sudden unconsciousness and coma, became pale and cyanotic, frothed at the mouth and gasped for air. There were no convulsions.

A catheterized specimen of urine obtained at this time was alkaline in reaction; specific gravity 1.018. It contained a trace of albumin, an occasional hyaline and granular cast, occasional white and red blood cells, and epithelial cells. Glucose and acetone absent.

In spite of all that could be done for the patient, she failed to respond and at 11:45 A.M. or exactly five and one-half hours from the time of admission, she died undelivered. The total duration of labor was twelve hours and fifteen minutes.

Necropsy (Dr. A. Plaut).—Gross Observations: The brain appeared relatively small. It weighed 1,215 gm. The outside of the brain except for hyperemia was not very remarkable. The floor of the third ventricle was slightly bulging, and there was a blue sheen directly behind the infundibulum. On the left side of the pons posteriorly there was an irregularly oblong flat hemorrhage 1.5 by 0.4 mm. Indistinct, bloody areas were seen over the cerebellum. The brain was cut frontally

artificial respiration including CO₂ and oxygen, intracardiac injection of adrenalin, and the use of the pulmotor, the patient began to breathe, and there was a return of pulsation in the radials. During this time, the patient continued in deep coma and was unconscious. At no time did she have anything resembling a convulsion. The pupils were fixed, dilated, glassy, and did not react to light. There was bilateral loss of corneal sensation. At 12:30 P.M., August 20, the pulse began to lose volume. A continuous intravenous injection of glucose and saline was given, and 300 c.c. of blood by direct transfusion. The patient continued to do poorly and she died at 1:30 P.M. (six hours and fifteen minutes after delivery).

Permission for an autopsy could not be obtained.

On lumbar puncture post mortem, the cerebrospinal fluid was uniformly pink in all three tubes. There was no clotting of the blood and when it had settled the supernatant fluid remained quite yellow. Microscopically, the spinal fluid contained 6,880 R.B.C. per c.mm. A cisternal puncture corroborated the above findings.

Comment.—Whereas the most conclusive evidence of subarachnoid hemorrhage is afforded by the state of the cerebrospinal fluid, this did not aid us in distinguishing the source of the hemorrhage, whether it was of primary meningeal origin or whether it came from an intracerebral hemorrhage which had broken through into the subarachnoid space. Accurate differential diagnosis in comatose patients between cerebral hemorrhage and subarachnoid hemorrhage is difficult. The foregoing case presented several features characteristic of intracranial aneurysm with rupture. 1. The patient was relatively young (25 years of age). 2. The blood pressures were low, varying from 108 systolic and 80 diastolic to 116 systolic and 80 diastolic. 3. There was no evidence of clinically discoverable disease such as arteriosclerosis, local or general infection or endocarditis. It is in cases of this sort that one expects to find rupture of a congenital aneurysm if autopsy is performed.

SUMMARY AND CONCLUSIONS

1. Three cases of maternal intracranial hemorrhage complicating labor have been described. Death occurred as a result of this hemorrhage in two cases. In one the autopsy revealed a large pontine hemorrhage; in the other, the post mortem was not done, but lumbar and cisternal punctures showed the presence of blood in the subarachnoid space. The remaining patient is still alive.

2. Subarachnoid hemorrhage may be due to congenital defect or weakness of the vessels, mycotic aneurysmal disease of the cerebral vessels, and hypertensive disease.

3. Spontaneous subarachnoid hemorrhage is most frequent in young persons suddenly stricken while in apparent perfect health. Congenital aneurysm undoubtedly is the underlying factor in the majority of cases. Leakage of blood into the subarachnoid space at the base of the brain gives rise to clinical signs upon which the diagnosis of this occurrence may be made with reasonable certainty. The presence of blood in the cerebrospinal fluid aids in confirming the diagnosis.

4. No history of toxemia or hypertensive disease could be obtained in our group; contrary to the cases reported in literature where there was a definite association between this syndrome and toxemia of pregnancy.

5. We found no causal relationship of ruptured intracranial aneurysm to pregnancy itself except so far as this pregnancy might have tended to elevate the blood pressure either by the strain of labor or the use of oxytocic drugs. Therefore oxytocics should be avoided during labor in patients suspected of intracranial aneurysm. These drugs prob-

Fundi normal. No cranial nerve palsies. Corneal and palatal reflexes were active and equal. No motor paralysis. Deep reflexes were active and equal. No pathologic reflexes. Abdominal reflexes not obtained due to post-partum abdominal relaxation. She complained of severe occipital and retro-orbital headache when aroused. There was marked rigidity of the neck. Left Kernig sign present. Lumbar puncture yielded uniformly bloody fluid which did not clot. Xanthochromia developed on standing. Her temperature was normal, the pulse 84 and regular, respirations 18, slightly irregular. The diagnosis by Dr. E. D. Friedman was then definitely made as subarachnoid hemorrhage probably due to the rupture of an intracranial aneurysm. Ergot and pituitrin injections may have served as precipitating factors.

On March 30, the second day post partum, the patient still complained of headache, appeared very restless, irritable, somewhat stuporous and disoriented. She had definite nuchal rigidity. Discs were slightly blurred, nasally.

On April 1, the fourth day post partum, the patient appeared more stuporous. The temperature rose to 102.8° F., the pulse ranged between 60 and 70, respirations 24. There was marked cervical rigidity and bilateral Kernig. Lumbar puncture was performed and 15 c.c. of bloody fluid under low pressure was removed. The supernatant fluid was orange colored.

On April 3, the sixth day post partum, her condition remaining about the same for several days, another spinal tap was done, and 15 c.c. of cherry colored fluid was withdrawn.

On April 6, the ninth day post partum, the temperature dropped to a normal level. The pulse was 80. There was a rapid regression of signs. The patient appeared rational and answered questions readily. The reflexes were normal.

Thereafter, the patient made a gradual but uninterrupted recovery and was discharged from the hospital on June 3, 1936, sixty-seven days post partum in apparently good health. The neurologic examination on the day of discharge was completely negative and clear cerebrospinal fluid was obtained. She was requested to report for further observation at regular intervals. When last seen in the Follow-up Clinic on Dec. 21, 1937, she complained of headache and dizziness.

Comment.—This case represents a cerebral aneurysm probably caused by congenital weakness of the vessel wall. The headache of three years' standing may have been due to the presence of the aneurysm acting as a tumor, or possibly, to its intermittent leakage.

The possibility must be kept in mind that ergobasine and pituitrin, the drugs used, may have been but a precipitating cause of leakage from an aneurysm or damaged wall under the strain of hypertension.

CASE 3.—B. K., aged 25 years, para 0, gravida i, appeared for examination on Jan. 22, 1936, at the second month of her pregnancy. The past history was unessential. The patient had enjoyed good health all her life. Menses began at 12 years of age, occurring regularly every thirty days, lasting five days. She last menstruated Nov. 16, 1935. The expected date of confinement was Aug. 13, 1936. The physical examination was negative. The heart and lungs were normal. Height 59 inches. Weight 99½ pounds. Pelvic measurements ample. Blood pressure was 110/80. The urine was normal. Blood Wassermann was negative. Subsequent ante-partum examinations revealed the same findings. Onset of labor occurred at term, on Aug. 19, 1936, at 6 P.M. The patient was admitted to the hospital at 10:35 P.M. The vertex was engaged in L.O.A. position; the cervix was two fingers dilated; the fetal heart heard in the L.L.Q. and in good condition. On Aug. 20, at 4 A.M. examination disclosed the cervix to be fully dilated; the vertex at the spines; the fetal heart in good condition; and pains occurring every three minutes, strong and regular. She delivered spontaneously on August 20, at 7:15 A.M. Medioclateral episiotomy was performed. Weight of baby was 7 pounds 2 ounces. The total duration of labor was thirteen hours and twenty-five minutes. Pituitrin and gynergen, 1 c.c. each, were given. Light gas and oxygen anesthesia was started.

Approximately ten minutes after delivery of the placenta, and prior to the completion of the episiotomy repair, the patient suddenly became cyanotic, rapidly comatose, respirations ceased; the heart became inaudible, and there was complete disappearance of the pulses simultaneously in both radials. After continuous

DISCUSSION

DR. EMANUEL D. FRIEDMAN.—Dr. Moskowitz has called attention to a symptom complex which is not at all unusual in neurologic wards. I think it was well worth while for him to have brought this subject before the obstetrician because for a long time even the medical man was not conversant with this syndrome. Many a house officer was blamed for being unskilled in obtaining spinal fluid because he got a "bloody tap" and frequently he was called to task for disturbing the general management of a case, by the introduction of this extraneous factor; but it soon became evident to most of us that these "bloody taps" were not all due to hemorrhage at the time of puncture. As Dr. Moskowitz said, the type of fluid obtained in these cases is quite different from that which one gets in cases of simple trauma from tapping of the vein at the time of puncture. In the latter instance, the first tube of fluid will be bloody and the subsequent tubes become more and more clear, whereas in true subarachnoid hemorrhage all the tubes are uniformly bloody. If one allows the fluid to stand in the tube, in cases of traumatic admixture of blood, one sees the formation of a clot, while in cases of subarachnoid bleeding there is no clot formation. The reason for this is that the rent which takes place in the aneurysmal sac is quickly covered by fibrin deposit, and then all that happens is a seepage of red blood cells into the spinal fluid, *without fibrin*, so that one has characteristic fluid, which is full of blood and yet contains no fibrin and, therefore, does not clot. If one allows the fluid to stand, one gets various types of discoloration in the supernatant fluid to which Dr. Moskowitz referred. Today most house officers recognize when they are dealing with a case of traumatic admixture of blood and when they are dealing with a case of true subarachnoid bleeding.

As Dr. Moskowitz has well said, syphilis seldom plays a role in these cases. In our experience, which has been fairly large, I know of only two or three instances in which we obtained a positive Wassermann in the blood, and they were all in colored patients.

As a rule, the etiologic factors concerned are those given by Dr. Moskowitz, namely, hypertensive disease and mycotic aneurysmal disease of the cerebral vessels and, finally, there is the group of young people who suffer from so-called congenital aneurysms. These are the cases that used to come to the post-mortem table of the late Dr. Charles Norris, Chief Medical Examiner of New York City, young persons suddenly stricken while in apparent perfect health with coma immediately supervening and rapid death. If the base of the brain is examined in such cases, one finds a sac which takes origin from one of the blood vessels forming the circle of Willis. In some instances, the medical examiner cannot be sure, but suspects that he is dealing with such an eventuality.

When the aneurysm has ruptured, the diagnosis is fairly simple. Most of us recognize this entity. The patient develops headache, vomits and goes into stupor or coma, depending upon the size of the rent in the vessels, the pulse becomes slow, and the individual exhibits no focal signs such as one sees in intracerebral bleeding. After a few days, if the hemorrhage does not terminate fatally, there develops the secondary stage, a meningeal syndrome, which is a reaction to the presence of blood in the subarachnoid space. It is really a foreign body meningitis. If the case is seen during this stage, one finds fever, leucocytosis, stiff neck and a positive Kernig, and one is led to think he is dealing with a case of infectious meningitis until he puts a needle in and obtains the characteristic fluid. As a rule, the patients who do not succumb immediately to a fulminating hemorrhage get well, and after ten or twelve days leave the hospital; as Dr. Moskowitz said, they may go through three or four episodes of such subarachnoid bleeding and experience no more episodes.

In the case of rupture, the diagnosis, as I have already stated, is not difficult; but prior to rupture it is somewhat more difficult to make the diagnosis. There are, however, a few symptoms and signs which may lead one to suspect the presence of an intracranial aneurysm. These are oculomotor paralysis involving the third or sixth nerve, a certain amount of trigeminal pain in the distribution, particularly of the upper branch of the fifth nerve, some disturbance of the sense of smell on the affected side, and possibly interference with vision on that side.

ably serve as precipitating factors (Case 2). The routine administration simultaneously of two oxytocic drugs, such as pituitrin and gynergen in doses of 1 c.c. each, following the third stage of labor should be avoided. Their indiscriminate use may lead to rupture of a congenital intracranial aneurysm even though this condition is not suspected (Case 3).

6. Patients who give a history of persistent or chronically recurring headache, or other prodromata prior to or during pregnancy and labor, when there are no signs of clinically discoverable disease, require the strictest watchfulness by those attending the case. It is advisable to make an ophthalmoscopic examination whenever a patient complains of headache. A complete neurologic examination will do away with many of the diagnostic errors. Incidentally this was not sufficiently stressed in two of the cases.

7. If the diagnosis of aneurysm can be made, it may be advisable to spare the patient the hazard of labor by cesarean section, in the hope that this may ameliorate the mother's condition, inasmuch as repeated leakage or recurrence of hemorrhage under stress usually occurs with these lesions.

8. The patients who recover should be periodically examined and cautioned against exertion of any nature.

9. A study of the literature shows that cases of spontaneous subarachnoid hemorrhage are frequently encountered in neurologic wards. The infrequency of subarachnoid hemorrhage complicating labor is established so far as published reports are concerned. It is our belief that it occurs more frequently than is generally appreciated. The failure to report intracranial aneurysms oftener may be due to the fact that they are being overlooked.

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KRUKENBERG TUMOR COMPLICATING PREGNANCY*

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UP TO the present time, some 90-odd cases of Krukenberg tumor have been reported in the literature. None of them, so far as I can ascertain, showed pregnancy as an associated condition, or complicating factor. For this reason I wish to report the following case:

Mrs. N. K., white, aged 33 years, para iii, was admitted to the First Obstetrical Service, Methodist-Episcopal Hospital, on Nov. 23, 1935, acutely ill, complaining of vomiting, weakness, and loss of weight for the past three weeks.

Her last menstrual period occurred June 16, placing her approximately in the fifth month of gestation. There was no history of hyperemesis or other toxic symptoms with the previous pregnancies, and delivery and puerperium were uneventful. The menses were always normal, her family and past history irrelevant. She had always considered herself a healthy individual. In the middle of October, 1935, about 5 weeks before the onset of the present illness, the patient had noted a painless lump in the left breast, with a subsequent black discharge from the nipple. A short time thereafter a mass appeared in the right breast. Both masses had steadily grown larger during pregnancy.

The first trimester of this pregnancy had been uneventful, and the onset of her present illness began about November 2, three weeks prior to admission. She then became nauseated, began to vomit, and was unable to retain any solid foods or liquids. There was a rapid loss of weight, and she felt weak.

On November 9, one week after onset, she was admitted to King's County Hospital with a diagnosis of toxemia of pregnancy. X-ray of the abdomen on November 19 showed evidence of one fetus and a questionable second. It was also felt that hydramnion was present, because of excessive size of abdomen for the time of pregnancy. At her own request, but against advice, she was discharged somewhat improved, November 20, eleven days after entering the institution.

Because of continuous vomiting, anorexia, and loss of weight, she was admitted to the Obstetrical Service of the Methodist-Episcopal Hospital, November 23.

Physical examination on that day revealed a seriously ill, pale, emaciated woman appearing much older than the stated 33 years. Lips and mouth were dry, tongue coated, teeth markedly carious, and there was a strong acetone odor to the breath. The breasts were rather small, and in each was found a hard, somewhat irregular, nontender, freely movable mass. The right measuring about 6 by 8 cm., and the left 4 by 7 cm. There was no discharge from either nipple. Both axillae presented several almond-sized nodes. The lungs were clear and the heart negative except for tachycardia.

Relaxation of the abdominal walls was marked, with considerable diathesis of the recti muscles. Her abdomen which was enlarged to the size of a seven months' pregnancy, revealed two indistinct masses, apparently arising from the pelvis. They were rather irregular in outline, and the one on the left side was larger than that on the right. A definite fluid wave could be felt. No fetal heart was heard.

Pelvic examination showed a relaxed vaginal wall, bilaterally lacerated and eroded cervix. The uterus could not be clearly defined from the two masses, but it was thought she was 5 to 6 months' pregnant. Reflexes were normal and there was no edema of the extremities. Temperature on admission was 98.6° F., pulse 90,

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I had the privilege of observing a case of intracranial aneurysm in which the diagnosis had been made *intra vitam* and the subsequent course of events proved the diagnosis to be correct.

If one finds a hemianopsia in such a case, it is additional evidence of the presence of a possible aneurysm, but many of these patients, as Dr. Moskowitz has said, go through life without ever having symptoms pointing to an intracranial lesion, except perhaps chronically-recurring headache.

In the first case reported by Moskowitz the periodic attacks of syncope antedating the final insult seemed to point to a constitutional dyscrasia, possibly similar to what Osler called poor tubing, a vascular dyscrasia in the patient which ended in hemorrhage into the pons. These aneurysms usually do not occur in the substance of the brain stem or the brain, but commonly take their origin from one of the branches that go to make up the circle of Willis, and are usually at the base.

In the second case the diagnosis was clear, the patient ran a typical course and recovered.

In the third case also I believe the diagnosis was justified. This type of case is similar to the ones which come to the medical examiner's office. In these cases it is necessary to make a diagnosis between intracerebral bleeding and rupture of an aneurysm. In this connection, if there are pronounced meningeal signs, the likelihood of rupture of an intracranial aneurysm is greater than if there are no meningeal signs.

Parenthetically, may I say that the abolition of the corneal reflex in cases of stupor is of considerable diagnostic significance. This reflex is usually abolished on the side of the hemiplegia. In the absence of other clear evidence of a cerebral vascular accident, I have found this sign very helpful. It is particularly useful in the so-called acute cases that come to the hospital with the diagnosis of either acute alcoholism or some other form of intoxication.

In closing, I think it was well worth while for Dr. Moskowitz to have brought this symptom complex before this group, and I agree with his conclusions, except that one would have to repeat what he said and what I have already hinted at, namely, that a diagnosis of intracranial aneurysm prior to rupture is exceedingly difficult unless it takes origin from the internal carotid or one of the branches of this vessel and gives rise to trigeminal pain and the ocular palsies to which I have referred.

Schultze-Rhonhof: On the Treatment of Pruritus Vulvae, *Zentralbl. f. Gynäk.* 61: 610, 1937.

The actual cause of this condition is not definitely established, and for this reason many methods of treatment have been adopted with varying results.

The author for many years had a patient, now 73 years old, under his care who suffered from most intractable pruritus. Anesthetic ointments, balsams, powders, painting with silver nitrate solutions, resorcin pastes and sitz baths of various kinds, vitamin A and ovarian preparations, and x-ray therapy were all equally ineffective.

Finally, in desperation, the author instructed the patient to coat the vulva with fresh honey. Improvement was obvious within a few days and continuation of the nightly application over a period of some weeks was followed by disappearance of the intense itching which did not recur even after the treatment was discontinued.

Since then the author has tried this therapy for numerous cases of pruritus with the same satisfactory result. He feels unable to give any satisfactory explanation for the efficacy of honey.

J. P. GREENHILL.

uterus was 18 cm. long and contained a five months' fetus. The left ovary was replaced by a large tumor, weighing 4,200 gm., and measured 26 by 20 by 16 cm. It was divided into several large lobes, and was enclosed in a fibrous membrane. On

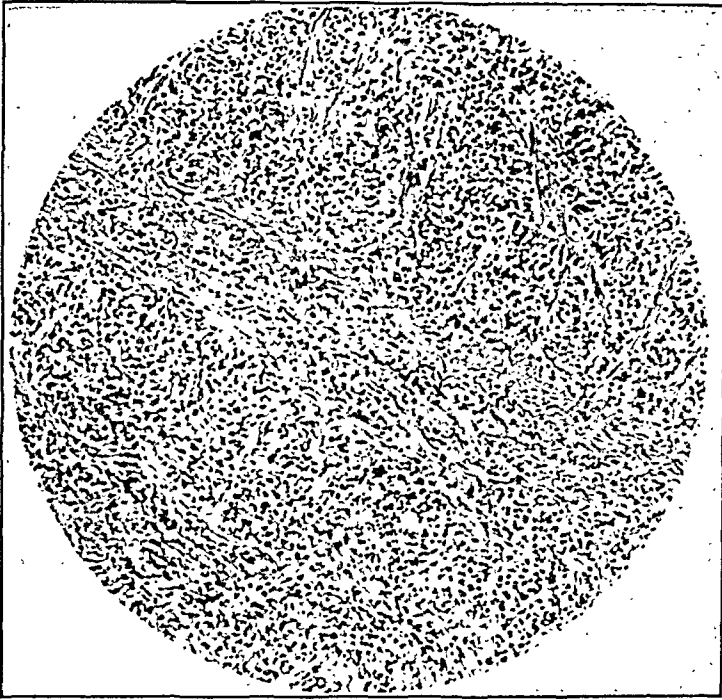


Fig. 2.—Photomicrograph of section of stomach.



Fig. 3.—Photomicrograph of section of right breast.

section it was solid throughout. In some areas the cut surface was dark red, homogeneous and hemorrhagic, while in others it was mottled gray and yellow, and the tissue was soft, friable, and apparently necrotic. The right ovary was somewhat

respirations 20. Urinalysis showed faint trace of albumin, 4-plus acetone, 2-plus diacetic acid, many granular casts. The R.B.C. numbered 2,950,000, the W.B.C. 18,600, and Hg 55 per cent. Sedimentation time was fifty-five minutes. The blood chemistry was normal, and the Wassermann negative.

Clinical Diagnosis.—Pregnancy, with possible twins, toxemia, pelvoabdominal tumor, ascites, carcinoma of both breasts.

She reacted well the first day to 10 per cent glucose by vein, 5 per cent glucose by rectum, clyses, and nothing by mouth. When, however, fluids and frequent small feedings were begun twelve hours after admission, vomiting recurred. Hyperemesis continued despite treatment. Because of her desperate state, it was decided to terminate pregnancy, and on the afternoon of November 25, the membranes were ruptured, and a No. 3 Voorhees bag was inserted into the cervix. Following induction her condition became progressively worse, and she died six hours later.

Postmortem Examination.—The autopsy performed by Dr. E. B. Smith, showed in part the following interesting conditions: Each breast contained a large, asym-

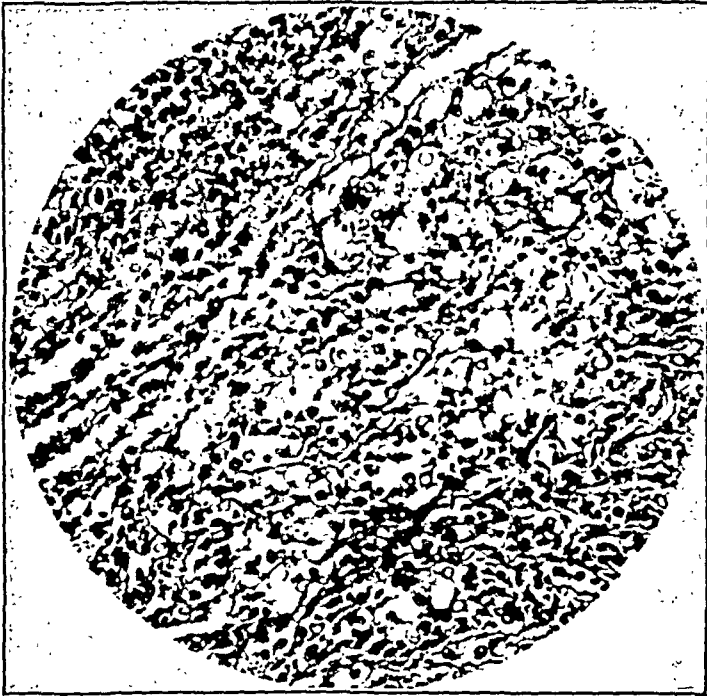


Fig. 1.—Photomicrograph of section of right ovary.

metrical, solitary tumor. The one in the right breast was 15 cm. in diameter, that in the left 10 cm. The tumors were circumscribed, but not encapsulated, and occupied all of both breasts. On section they were hard, white, and lobular.

Upon opening the peritoneal cavity, about 2,000 c.c. of brown fluid escaped. The mid-abdomen was filled with a large tumor which sprang from the left ovary. The stomach was normal in size and contained dark brown fluid. There was a tumor on the posterior wall 4.5 cm. from the pylorus. The growth was 8 cm. long, 4.5 cm. wide, and 0.5 cm. thick, and the edge was sharply outlined. The surface was smooth, white, and homogeneous. Near the pyloric end of the tumor was a crater 1 cm. in diameter and 7 to 8 mm. deep. The edge was sharply punched out, the sides were sloping, and the floor was covered with a yellow substance. In appearance it resembled a peptic ulcer. The remainder of the stomach presented normal rugae, and the mucosa was smooth and pale. There was a string of enlarged nodes along the greater curvature. On section these were firm, white, and homogeneous. The pancreas was of normal size and showed a gray, lobular structure. The

According to Gierke meconium peritonitis may be applied to those cases in which there is demonstrable within the peritoneum meconium, calcified meconium, mucous droplets, foreign body giant cells, cells from the source of perforation, fibrinous or fibrous adhesions, and rarely, lanugo hair. Boikan, Kornblith and Otani, and Dodd report cases of meconium ileus and in their papers review extensively the literature on the subject. Snyder, and Hall have studied the bacterial flora of the first specimens of stools of newborns and Snyder has done the same for meconium from stillbirths.

The senior author has been impressed by the observation that in cases of cesarean section meconium contamination of the spill into the peritoneal cavity or into the operative incision of the mother may lead to a peritonitis of varying degrees of severity, or to a delayed healing of the abdominal wound and a stormy convalescence. It is rather strange in view of the complete literature on the subject of meconium, that no one has thought of conducting experiments dealing with the pathologic and biologic properties of this material. The present communication is a report of investigations along these lines.

METHODS

The meconium used in these experiments was obtained on the maternity floor of Michael Reese Hospital from newborn infants at the time of delivery and was collected under sterile precautions. The scope of the work may be divided as follows:

1. *Toxicity experiments:* Minimal lethal dose in rats and the effect of a filtered solution of meconium when injected intravenously upon the blood pressure and respiration of anesthetized dogs.
2. *Effects of meconium administered intraperitoneally, intramuscularly, and subcutaneously to rats and dogs.*
3. *Effects of instillation of unfiltered meconium into the uterus of dogs.*
4. *Bile controls:* Since biliary tract products are among the chief constituents of meconium, it was deemed advisable to repeat certain of above experiments using bile instead of meconium. The bile used was sterile upon culture and was procured from fresh human autopsy material.

RESULTS

Toxicity Experiments.—Five rats were injected intraperitoneally with varying amounts of sterile undiluted meconium (from $\frac{1}{4}$ to 1.5 c.c.) by means of a syringe and an 18 gauge needle. Objectively the rats were well and at autopsy three days later the abdominal cavities of the rats showed the following changes: the omenta were somewhat discolored, the abdominal cavities contained a small amount of fluid and bits of inspissated meconium clung to and stained some of the intestinal coils.

In two dogs under nembutal anesthesia, it was observed that small amounts of a filtered suspension of meconium in saline solution injected intravenously caused a marked and prolonged depression of blood pressure and an increase in amplitude and frequency of respiration as is seen after the injection of bile; a somewhat larger dose was fatal, the dogs not recovering from the effect and dying from heart failure.

Effects of Intraperitoneal, Intramuscular, and Subcutaneous Injection.—Three grams of meconium were thoroughly mixed in 15 c.c. of sterile saline and 5 c.c. of the mixture injected intraperitoneally into each of three female rats. One week later the rats were normal to outward appearances and were autopsied. The abdominal cavities contained a slight amount of murky fluid and the omenta had a dirty yellowish discoloration and also seemed somewhat contracted and matted together. Microscopic examination of the omentum revealed areas of myxomatous

enlarged, but the normal contour was well preserved. It measured 4.5 by 3.5 by 2 cm. On section most of the ovarian tissue was replaced by a white, uniform growth. The tubes appeared normal.

Microscopic Examination.—*Stomach:* In the ulcerated area the mucosa was replaced by a new growth, most of which had sloughed away, leaving a narrow rim of partly necrotic tumor tissue lying above the muscularis mucosae. The growth was composed of epithelial cells of variable size and shape, with granular acidophile cytoplasm, and dark oval nuclei. At the edge of the tumor the mucosa was replaced by diffuse carcinoma, supported by a delicate stroma. The cells were large, polyhedral with opaque, acidophile cytoplasm and eccentric nuclei. A few of the latter were crescent shape. Many of the cells were degenerated. Groups of tumor cells were also found in the muscularis. *Right Ovary:* The sections showed small groups of tumor cells enclosed in a network of delicate fibrous tissue. The cells were round or oval, enlarged, pale, with crescentic nuclei pushed to the edge of the cell, forming typical signet ring cells. *Left Ovary:* All of the sections showed the same kind of cells as in the stomach and right ovary. *Breasts:* The gland tissue in both was proliferating, and the picture was approaching that seen in the lactating breast. The stroma was infiltrated with groups of tumor cells, like those previously described. In the Fallopian tubes some of the lymphatics in the wall were filled with tumor cells resembling those found elsewhere.

Pathologic Diagnosis.—Diffuse ulcerative carcinoma of the stomach, bilateral secondary Krukenberg tumor of the ovaries, bilateral secondary Krukenberg tumor of the breasts, with metastases in the Fallopian tubes and pancreas.

Was the primary tumor in the stomach or ovary? Histologic examination points to a gastric origin. Most recent writers feel that Krukenberg tumors are usually secondary to carcinoma of the stomach or intestines. Ewing believes that "the pure Krukenberg tumor is always secondary." However, proof as to origin, structure, and manner of transmission are still lacking.

Summary.—The case here reported shows characteristic Krukenberg tumors of both ovaries and breasts, with involvement of other organs, and a probable primary focus in the stomach. It is especially interesting because of the brief duration and paucity of symptoms, and its association with pregnancy.

THE PATHOLOGIC PROPERTIES OF MECONIUM*

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THE general textbooks on obstetrics and pediatrics contain scant reference to meconium beyond the fact that it is the first excreta of the newborn, and perhaps enumerate the various constituents of meconium (Williams¹). The clinical literature, on the other hand, has a considerable number of papers which deal with the various physical and chemical properties of meconium (Sheldon and Ramage, Passini, Norton and Shohl, Giaume and Lanza), and more particularly with its pathologic manifestations as is occasionally seen in cases of meconium ileus or peritonitis in the newborn.

*Read at a meeting of the Chicago Gynecological Society, December 17, 1937.
Aided by the B. Smoler and Otto Baer Funds.

tion of the thigh to palpation, the tissues were bile stained, and upon exposing the abscess it was seen to be a firm nodule the size of a pea, the center of which was necrotic tissue. The animal which was sacrificed on the eighth day showed nothing grossly beyond yellowish discoloration at the area of injection, but upon microscopic examination localized areas of granulation tissue were seen; the connective and areolar tissue contained many lymphoid elements and a small lymph node present was definitely hyperplastic.

Subcutaneous Injection.—Each of two rats was injected with 0.5 c.c. of bile subcutaneously in the right flank. At autopsy one week later the sites of injection revealed naught beyond discoloration by the bile, and histologic examination was essentially the same in both, to wit: diffuse round cell infiltration, edema, hyalinization, and areas of hyperemia and extravasation of blood.

DISCUSSION AND CONCLUSIONS

It should be emphasized first that all samples of meconium used in experiments were sterile to bacteriologic culture and any effects observed are due to the substance under investigation and not due to bacterial contaminants. A review of the protocols shows that meconium possesses definite toxic properties of a low grade nature, very similar to those of bile, but much more pronounced in its local effects than bile. This perhaps is due to certain of the constituents of meconium such as lipoids, lanugo hair, epithelial debris, etc., which lend to it its viscid gelatinous consistency, and explain more intense, irritating local action, viz.: Intramuscular and subcutaneous abscesses are much more marked and localized in case of meconium than in case of bile. It has been seen that intraperitoneal injection of meconium into rats is invariably followed by definite pathologic sequelae, such as omental reaction, serous exudation, etc., and at the same time one must keep in mind the fact that rats are notoriously resistant to the ordinary human infections. Bile is very toxic when administered intravenously and a filtered meconium suspension possesses the same property to a lesser degree, since the latter contains less of the bile salts than does pure liver or gall bladder bile. An important fact is, that meconium may produce adhesions in places where it is carried by peristalsis (see experiments on dogs).

The principal practical value of this work concerns its application to the technique of cesarean section. Adequate protection of viscera and peritoneal surfaces is omitted by many operators and suction apparatus may be inadequate or unobtainable. Fortunately, contamination with meconium is not frequent and when meconium escapes in semisolid form, it may easily be wiped away, but when a considerable amount of amniotic fluid with much meconium in suspension gushes into the field of operation, the tissues become bathed in the mixture. The occasional case demanding cesarean section when intrapartum infection exists should be especially safeguarded since meconium encourages adhesions in general as well as infection and suppuration in the operative field. When a large amount of amniotic fluid is demonstrable, vaginal rupture of the membranes may be done in order to forestall any possibility of spill of the liquid contents into the peritoneal cavity.

connective tissues containing masses of polymorphonuclear leucocytes; occasional round cells were seen. The nuclei of the connective tissue elements varied considerably in chromatin content, frequently containing nucleoli and mitotic figures. Diagnosis: marked proliferation of connective tissue, apparently in response to a chronic inflammation, and early scar tissue formation.

A young 20 pound male dog was injected intraperitoneally with 20 c.c. of a thick suspension of meconium in saline; the dog showed no untoward effects and was killed and posted on the fifth day following injection. *The gross findings:* the peritoneal surfaces were smooth and shiny but the abdominal cavity contained about 60 c.c. of a somewhat turbid dirty yellow fluid; the omentum was hyperemic and somewhat reddish brown in color; spleen slightly enlarged and moderately firm; the upper surface of the right lobe of the liver contained a bit of inspissated meconium and was adherent to the diaphragm by soft adhesion. Microscopic examination revealed moderate hyperplasia of the spleen, and swelling and degeneration of the tubular elements of the kidney. The area of diaphragm adherent to the liver contained a fibrinous exudate upon its serous surface and enmeshed in the fibrinous network were scattered clumps of both round cells and polymorphonuclear leucocytes.

Intramuscular Injection.—One cubic centimeter of an unfiltered boiled 10 per cent suspension of meconium was injected into the right thigh of a rat. The animal developed a palpable abscess and was killed two weeks later. An abscess measuring about 1 by 1 by 1 cm. was situated in the muscles of the medial aspects of the thigh; the abscess contained a thick brownish yellow material very much like an admixture of pus and meconium. Histologically the abscessed area contained many round cells and degenerated muscle fibers and nuclei; a wall of leucocytes and connective tissue cells surrounded the area of necrosis, and even beyond the walling-off process muscle fiber showed degeneration.

Subcutaneous Injection.—One cubic centimeter of the above suspension was injected into the flank of another rat, and it too was killed two weeks later. At autopsy the animal had a subcutaneous abscess which also extended into the deeper tissues. The area measured 2 by 2 cm., appeared grayish yellow in color, and resembled a localized cellulitis. *Pathologic diagnosis:* chronic organizing inflammatory reaction with prevalence of round cells; infiltration of adjoining muscle tissue by round cells and disintegration of muscle fiber.

Instillation of Unfiltered Meconium Into the Uterus.—After performing laparotomy, the uteri of two dogs were incised (about one inch) and the right uterine horn in each case was soiled with several bits of sterile meconium. The uterine incisions were then closed in the usual way and the animals killed on the fifth and tenth days, respectively, following the operation. The autopsy findings are essentially the same for both animals; the right horn is encased by soft adhesions, the serosal surface in the region of the incision is markedly injected and enlarged in comparison with the left horn. Upon opening the uterus, the lumen was filled with a thick brownish material and grossly the mucosal surfaces of both horns seemed similar. Microscopically, the infected horn showed evidences of an acute inflammatory reaction, viz., fibrinous plaques with clumps of leucocytes, edema and round cell invasion of the superficial layers of the endometrium.

Bile Controls.—Toxicity experiments. A series of rats were injected intraperitoneally with graded amounts of sterile human bile ($\frac{1}{2}$ to 2 c.c.). The rats seemed normal and were killed at intervals of from three to ten days after injection. A typical protocol: the peritoneum was shiny, but the blood vessels were prominent; the abdomen contained a small amount of clear fluid and several of the intestinal coils were bile tinged; soft adhesions of omentum to liver. *Microscopic examination:* A number of round cells were present in the omentum and several areas of hyaline-like material were found. The spleen was hyperemic and somewhat hyperplastic.

Intramuscular Injection.—Each of two rats received 0.5 c.c. of bile into the thigh muscles of the right hind leg; the rats were killed, seven and eight days following injection; the one killed on the seventh day had gross enlargement and indura-

In a review of the literature on this subject, one is impressed with the comparative dearth of material and the infrequency with which articles have appeared in our journals.

I desire therefore to report the following case of puerperal sepsis, treated at the Beth-El Hospital, Brooklyn.

Case 89599.—L. Z., aged 22, white, primigravida, ante partum course essentially negative. Pelvic measurements relatively ample. Past medical history negative except for appendectomy about one year prior to present pregnancy, with uneventful convalescence. On Aug. 6, 1937, after a labor of nine hours and fifty minutes, patient was delivered spontaneously of a living male baby (weight 6 pounds, 14 ounces) in L.O.A. position. A right mediolateral episiotomy was repaired. At the end of labor, temperature 100.4° F., pulse 68, respirations 22, blood pressure 100/80. After thirty-six hours, patient had a chill, complained of soreness throughout the body, associated with a dry hacking, unproductive cough. Temperature 103.4° F., pulse 120, respirations 24. Physical examination at this time revealed no intra-abdominal or intrathoracic lesion.

Second day after delivery: Temperature 107.2° F., pulse 100, respirations 28. Medical examination was negative except for moderate tenderness in both lower quadrants. Urinalysis negative. Lochia foul. R.B.C. 3,500,000, Hg. 70 per cent, W.B.C. 18,000. Polymorphonuclears 84 per cent and monocytes 16 per cent. Blood culture (aerobic) negative after forty-eight hours.

Third, fourth, fifth days after delivery were marked by severe chills, occurring as often as every eight hours, followed by temperatures ranging from 105° to 108.4° F. In spite of this hyperpyrexia, the patient did not appear to be acutely ill, except for labial cyanosis. A second aerobic blood culture proved negative. Repeated physical examinations were negative.

On the sixth day, anaerobic blood culture was returned *positive* for *anaerobic hemolytic streptococcus*. General condition remained the same for the seventh day, averaging two to three chills within twenty-four hours. However, on the eighth day, the patient was seized with a sharp stabbing pain, in the left axilla, radiating to the left shoulder. Patient became cyanotic and dyspneic and was racked by a paroxysmal cough, followed by a sanguineous expectoration. Examination revealed fine and coarse râles in the left axilla and a pleural friction to-and-fro rub. Impression: pulmonary embolism. The pulmonary distress and cyanosis made it imperative that the patient be placed in an oxygen tent for relief. For the next nine days the chills were neither so severe nor the temperature so high. On the eighteenth day, the following physical signs indicated a left pyopneumothorax. The patient was dyspneic, moderately cyanotic and extremely pale. The left chest was completely tympanitic with absence of vocal fremitus and breath sounds, anteriorly. Posteriorly and in the lower left axilla there was cavernous breathing and a metallic tinkle as well as a succussion sound. The area of cardiac dullness was tympanitic and the heart was displaced to the right. A needle was inserted in the left eighth interspace, at the angle of the scapula and 1,100 c.c. of a grayish purulent fluid with distinct putrid or colon odor was removed. Portable roentgenograph showed "a collapse of a hydropneumothorax on the left side with a fluid level extending from the base upward to the second interspace. The heart and mediastinum are displaced to the right. There is a proliferative infiltration noted throughout the right pulmonic field, mainly in the region of the right middle lobe, suggestive of bronchopneumonia." Two days later, on the twentieth day of illness, an open thoracotomy was performed along the left seventh rib. A large empyema cavity was found extending from the second interspace to the diaphragm, filled with putrid yellow pus. Culture of the pus revealed a mixed aerobic and anaerobic infection, but no hemolytic streptococcus.

The same general condition prevailed for the next thirteen days, chills, hyperpyrexia (in spite of the ample drainage from the thoracotomy), moderate dyspnea and occasional cyanosis. At this time, blood culture became negative and patient showed signs of improvement, which continued until the patient's discharge on the sixty-second day of illness and forty-two days after the thoracotomy.

SUMMARY

1. Meconium possesses a low grade toxicity and resembles bile in its pathologic properties, but produces a greater local inflammatory reaction than bile.

2. Our findings confirm and show a definite basis for the observation that the spill containing meconium escaping into the peritoneal cavity of the mother or into the operative incision may lead to a peritonitis, to adhesions, or to delayed healing of the uterine and abdominal wound.

3. This work emphasizes the necessity of adequate protection of all surfaces in the operative field from the contents of the amniotic sac when performing an abdominal cesarean section.

We are indebted to Dr. M. Corrigan for the histological studies and to Dr. H. Necheles, Director of G. I. Research, for advice and facilities offered.

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SEPSIS PUERPERALIS THROMBOPHLEBITICA PUTRIDA (SCHOTTMÜLLER SYNDROME)

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MANY investigators have, from time to time, noted and reported the presence of anaerobic streptococci, in the genital tract of normal pregnancies as well as in the uteri and blood stream in cases of postabortal and puerperal sepsis. Krönig, in 1895, demonstrated obligate anaerobic streptococci in the female genital tract, work that was corroborated by Menge and later by Stöhler and Winkler, who found anaerobic bacteria, for the greater part streptococci, in uterine cultures, in one-third of all their normal, fever-free post partums. Böhne was able to show the presence of anaerobic streptococci in the vaginal secretion of 20 per cent of his ante partum cases; these observations were confirmed by Natwig and Wegelius who found an even greater incidence. In America, Williams in 1898, Wadsworth and A. W. Lea, independently, confirmed the work hitherto reported.

It remained, however, for Schottmüller to arouse the curiosity of the obstetrician and gynecologist to more than mere academic interest in the detection and culture of this group of cocci, to observe the clinical picture produced by these bacteria, and to culture anaerobically all cases of postabortal and puerperal infection and thereby prove that hitherto negative aerobic cultures were very frequently positive when grown anaerobically.

Schottmüller's syndrome is characterized by: foul lochia (produced by putrid endometritis), high intermittent temperature, chills, many small or one large lung abscess (resulting from embolism), pneumonia, empyema, and other complications of bacteremia.

serted in the bladder and a probe guided in the same orifice posterior to the catheter and in the direction of the cervix. By rectal examination it was followed from the region of the cervix to near the obstruction, which felt about one-half inch thick. By rectal examination the cervix felt longer than normal, the uterus and appendages being normal. The patient was instructed to return for further examination at the next menstrual period. Inspection at this time showed menstrual blood coming from the apparent urethral meatus. The patient entered the hospital following the period of bleeding. Examination under anesthesia was essentially as noted above. A small dilator was placed in the sinus leading toward the cervix. With this as a guide, a small anteroposterior incision was made in the occluding tissue. By means of blunt and sharp dissection the incision was deepened until the posterior wall was penetrated. The little finger was inserted and revealed normal vaginal tissue. The dilator was brought into view and dissection carried out anteriorly until the dilator was freed. Inspection showed the urethral meatus to be recessed some-



Fig. 1.

what on the anterior vaginal wall. The excess tissue which was about three-eighths of an inch in thickness was trimmed and the raw edges approximated with sutures. A dilatation and curettage was done in the usual manner. The cervix was longer than normal, otherwise the internal genitalia were not remarkable. Subsequent follow-up showed a good reconstruction. (See Fig. 1.)

DISCUSSION

The possibilities for explaining this anomaly from the embryologic point of view are first, that the posterior bulbous portion of the hymen grew too far toward the urethra and that the lateral slits formed by the invagination failed to materialize, the inferior aspect of the hymen proliferating abnormally. Second, the fusion of the proliferating vaginal epithelium and urogenital sinus failed, and third, the plug of vaginal epithelium, which normally proliferates eccentrically and posteriorly, proliferated only toward the urethra. That the case presented is not an imperforate

Prontosil and prontosil were used, but we were compelled to discontinue their use because of occasional attacks of cyanosis which may have been caused by the pulmonary complications and not by sulphhemoglobinemia. Blood transfusions were employed but with little apparent effect. Total of 1,350 c.c. of whole blood in doses of 150 c.c. were given by the citrate method, particularly at the onset. Rivanol, one of the aniline dyes, much in vogue in the 1920's, was also utilized in an effort to combat this condition, but to no avail. All known methods of treatment had apparently been useless. Therefore, with a hope that so-called specific therapy might be effective, we obtained and injected intramuscularly convalescent scarlet fever serum, in doses of 50 c.c. every eight hours, for a total of 1,560 c.c.

I wish to express my deep appreciation of the hearty and willing cooperation of Dr. S. Levine of the Medical Department and Dr. B. Kogut of the Surgical Service in the treatment of this case. Also my thanks to Dr. A. Koplowitz for his permission to report this rare and interesting case from his service.

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201 EASTERN PARKWAY

APLASIA OF THE LOWER FEMALE GENITAL TRACT

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AN UNDERSTANDING of developmental anomalies and malformations of the lower genital tract of the female must of necessity take in account embryology. Four conceptions, namely, (1) that the lower vagina and hymen are Müllerian in origin; (2) that they are Müllerian and Wolffian in origin; (3) that they are totally derived from the urogenital sinus; (4) that they are Müllerian and urogenital, have been considered. Koff¹ has recently reviewed the literature and has presented excellent evidence from studying human fetuses that the upper four-fifths of the vagina are Müllerian in origin and that the lower fifth and the hymen are formed from the Müllerian ducts and the sinovaginal bulbs, the latter arising from the epithelium of the urogenital sinus. The hymen is made up of two lateral lips and an inferior segment. The inferior segment is disc-like. Internally it is lined by stratified squamous epithelium of the vagina and externally by the stratified columnar epithelium of the urogenital sinus. Between these two epithelial coats is the compressed stroma of the vagina and urogenital sinus. Koff's¹ conception of the embryology of this part of the female genitalia seems clear-cut, and the following case is presented as a developmental anomaly based on his findings.

The patient is a forty-year-old single female who complained of irregular and profuse menstruation for the past three months. Bleeding was accompanied by the passage of clots, bright red blood, and dysmenorrhea, none of which she had previously experienced. There were no menopausal symptoms or symptoms of hypothyroidism. Neither was there any other vaginal discharge. Local examination revealed normal appearing external genitalia. Further inspection showed no hymenal opening and a urethral meatus somewhat larger than normal. A catheter was in-

2 or 3 cm. above the left Poupart's ligament. This was dull to percussion but sensitive to touch. Pelvic examination revealed an intact vaginal introitus. On rectal palpation the cervix was found to point anteriorly. The uterus was normal in size, retroverted and crowded over to the right. A tense, cystic globular mass about 6 or 7 cm. in diameter filled the left fornix and encroached upon the cul-de-sac. The laboratory data were not unusual. A diagnosis of left ovarian cyst was made.

Under ether anesthesia laparotomy was performed on Feb. 24, 1937 through a mid-line scar 10 cm. in length. About 30 c.c. of serosanguineous fluid was found free in the pelvic cavity. The uterus was small and pubescent. The right tube and ovary were normal. A Morgagni cyst about 2 cm. in diameter was found in the outer end of the right broad ligament. The left tube was converted into a retort-shaped structure, the dilated ampullar segment measuring about 5 cm. in diameter. Two twists were found at the junction of the middle and outer thirds of the tube, just external to the outer edge of the mesovarium. The wall of the tube distal to the site of strangulation was dark and hemorrhagic, the remainder was normal in color and appearance. The left ovary was normal in size and color. The left tube was untwisted, resected, and excised at its interstitial portion. The normal left ovary was retained. The raw surfaces were peritonized by the round ligament and the left ovary suspended. The Morgagni cyst on the right was resected and the posterior leaf of the broad ligament closed. The postoperative course was uneventful.



Fig. 1.—The tube is enlarged and dilated in its outer third. In this zone the color is blue black, the peritoneum lusterless.

The pathologic report follows: The specimen consisted of a retort-shaped tube measuring 13 cm. in length, 5 mm. at the uterine insertion and 6 cm. in diameter in its distal third (Fig. 1). The external appearance was varied. The inner two-thirds of the tube presented a smooth shiny peritoneal coat which was somewhat injected. At the junction of the middle and outer thirds there was marked angulation. The twist previously described at this point was not well defined, probably the result of operative handling and fixation. The outer third of the organ was hemorrhagic, blue gray, and lusterless. The fimbriae were retracted and the abdominal ostium as such was no longer recognizable.

The mesosalpinx in this zone was thickened and hemorrhagic. On section the dilated tubal segment was filled with blood which shelled easily from the underlying endosalpinx. The latter was smooth and blue gray in appearance. All folds had been obliterated. The tubal musculature was hemorrhagic and markedly atrophic. Through the inner two-thirds the lumen was normal and free from blood. The folds were grossly normal. The muscle was slightly edematous. The serosa was injected. Microscopically, section through the isthmus segment of the tube also included a zone of the muscular coat of the uterus. The tube lumen though narrow was normal and free from blood. The folds were short. The inner longitudinal muscle coat was well defined. The broad circular muscular coat was sharply differentiated and in turn was succeeded by a second longitudinal coat which fused with the uterine musculature. A zone of loose areolar tissue, however, intervened. This contained several vessels

hymen is shown by the fact that menstrual blood escaped through the apparent urethral meatus, and had the hymen been imperforate, the patient would have had a hematocolpos in her early menstrual life. McKelvey and Baxter² presented a case of marked developmental anomaly, part of which showed the vagina ending in a blind pouch caudally. This part they claim had all the characteristics of normal vaginal tissue. They fit their finding to Koff's¹ conception or that of Mijsberg³ the latter claiming that the lower part of the vagina is Wolffian in origin. Masson⁴ illustrates a case similar to the one presented. In his case there is less vagina caudally and a sinus connecting the vagina cephalad to the urethra. Similar anomalies occur in female pseudohermaphrodites and hermaphrodites of undetermined sex.⁵

CONCLUSIONS

A case of aplasia of the lower female tract is presented which is believed to be due to a failure of the proliferating epithelial plug of the vagina to grow posteriorly and a failure of fusion with the sinovaginal bulbs. That the inferior aspect of the hymen enters into the formation of the anomaly cannot be doubted.

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SEGMENTAL TORSION OF FALLOPIAN TUBE IN A YOUNG VIRGIN*

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TORSION in the Fallopian tube is uncommon and especially rare in the virgin. A review of the literature by McEachern in 1934, revealed only 9 cases. Additional cases in virgins are recorded by Stark, Davies, Rogers, Darner, Jefferson, Gillies, Corlette, Michon, Block, and Michael. A study in December, 1935 made by K. F. D. Waters revealed 17 recorded cases of tubal torsion in young girls, although in this paper virginity was not a prerequisite.

In the case abstracted below torsion has evidently occurred in a normal tube. This inference is supported by the age of the patient, virginity, and findings at operation.

Miss M. E., aged 19 years, single, was admitted to the Greenpoint Hospital on Feb. 17, 1937, complaining of pain in the left lower quadrant. Childhood diseases included diphtheria and scarlet fever. Menstruation began at the age of thirteen, was always regular and of a twenty-eight day type, and of three days' duration. The patient had typhoid fever in March, 1936 and was in bed for four weeks. This was followed by a period of amenorrhea for two months. Menstruation resumed in May, 1936 was accompanied by severe cramplike pains localized to the left lower quadrant. Since then, menstruation has occurred every twenty-one days, for six days. Pain in the left lower abdomen has since appeared three days prior to menstruation, persisting until two days after completion of bleeding.

Upon admission the temperature, pulse, and respirations were normal. Head, neck, and thorax revealed nothing of note. The abdomen presented an insensitive mass,

*Presented at a meeting of the Brooklyn Gynecological Society, March 4, 1938.

to the site of torsion. There was no evidence of inflammation. The opposite adnexa were normal. This case may be therefore viewed as one of segmental torsion and necrosis of a previously normal tube occurring in a young virgin.

1530 PRESIDENT STREET

MELANOMA OF THE VULVA*

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DURING the past year it has been the writer's good fortune to chance upon a very infrequent type of malignancy of the vulva, namely, malignant melanoma.

Mrs. M. I., a 76-year-old white woman, was seen in the Magee Dispensary complaining of "lumps" in the vulva and both inguinal regions. The patient stated that she had always had a small mole on the right labium majus. In October, 1932 she first noticed black "lumps" on the right vulva, which were painless. Four months later they began to bleed and were considerably larger. On Feb. 13, 1936, "lumps" were observed in the right groin, following three operations a month previously under local anesthesia. Six weeks before admission the patient felt additional "lumps" in the left groin. At this time she had had a serosanguineous vaginal discharge for about eighteen months. The "lumps" had been painful for about two years and were becoming progressively larger. She had lost only a slight amount of weight. Associated symptoms included headache, blurring of vision, tinnitus, and episodes of abdominal discomfort following ingestion of fried foods. The menstrual history was normal and the menopause occurred at the age of fifty. She had had two normal full-term pregnancies. The past medical history included typhoid, measles, influenza, and diphtheria. The family history was negative for malignancy.

There was marked wrinkling of the skin. The vessels were hard, tortuous, and sclerosed. She had complete dentures. The tonsils were enlarged. The heart was not enlarged but a few premature beats were noted. There was slight pretibial edema.

The vulvar lesion (Fig. 1) consisted of a large somewhat nodular mass, irregularly the size of a tangerine, occupying the entire right labium minor and of a purplish color. The lower surface of the mass presented some ulceration and extended out to the clitoris, prepuce, upper part of left labium minor, and had infiltrated through so that there were several pigmented spots, of various sizes, on the outer surface of the right labium major. There were large firm masses in both inguinal regions.

Laboratory findings.—The urine was negative except for a few white blood corpuscles. It was negative for melanin. Blood count: R. B. C., 3,690,000; W. B. C., 5,550; polymorphonuclears, 56 per cent; lymphocytes, 43 per cent. The blood sugar was 120 mg. Nonprotein nitrogen was 24.3 mg. Kahn was negative. Sedimentation time was 20 min.

Course in hospital.—On Dec. 21, 1936, under gas-ether anesthesia a biopsy was taken and four radium needles, containing 12½ mg. of radium each, were inserted directly into the vulvar mass, for a period of forty-eight hours (2,400 mg. hr. of radiation).

Pathologic Report From Biopsy.—The tumor (Fig. 2) was composed of a pleomorphic type of cell, varying from spindle cell type to a large epithelial type. The cells varied in their melanin content, some of them being melanin free, and others

*Read at a meeting of the Pittsburgh Obstetrical and Gynecological Society, February 7, 1938.

about which were collections of lymphocytes especially prominent about the veins. The muscle fasciculi of the uterus showed slight edema and capillary engorgement. Just beneath the perimetrium the capillaries contained an occasional polymorphonuclear leucocyte. About them too were moderate numbers of lymphocytes and occasional plasma cells. In the outer segment of the tube, distal to the point of torsion, the tube lumen was widely dilated. All the folds had been obliterated (Fig. 2). The lining epithelium and muscle fasciculi were all necrotic for the nuclear elements had disappeared and only cell shadows remained. Edema was evidenced by wide separation of the muscle cells and the presence of granular fibrin between the interstices. At the periphery a narrow segment of viable muscle and connective tissue fibers was found. Zones of interstitial hemorrhage were present. An occasional lymphocyte was encountered. The detached blood clot found in the tube lumen was free from chorionic villi. Torsion and necrosis of the distal third of the tube found at operation was accordingly confirmed. Inflammatory reaction in the viable segment was evidently secondary.

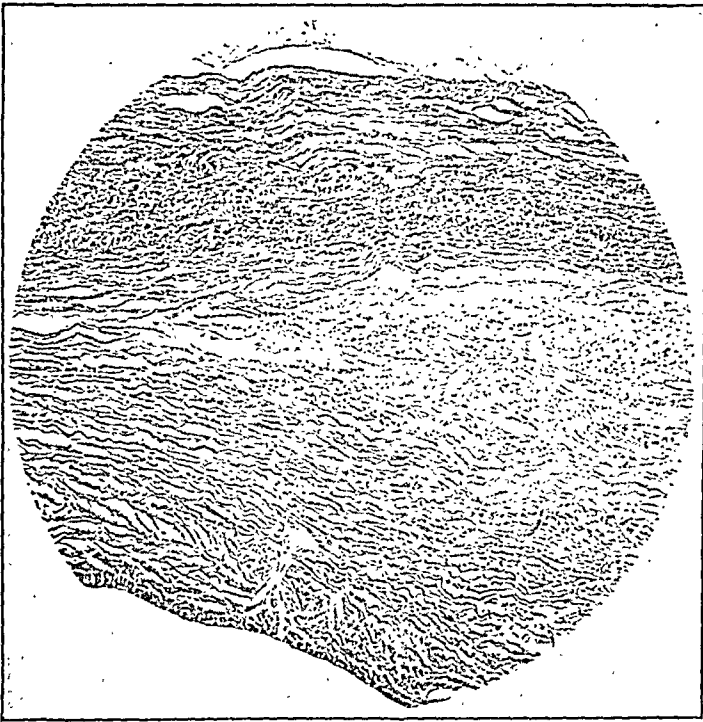


Fig. 2.— $\times 80$. A segment of tube wall through the dilated and necrotic ampullar zone. All folds have been obliterated. The muscle and connective tissue fibers are necrotic, only the cell shadows remain. No exudate is present. The blood clot was artificially removed from the tube lumen.

In retrospect, this case may be considered as one of torsion beginning with the first menstruation after an attack of typhoid fever, terminating in complete necrosis of the twisted segment. Pre-existing inflammation was not a factor, for the hymen was found intact and no pathology was present in the uterus and right adnexa. Furthermore the involved tube showed no evidence of inflammation in mucosa or muscle proximal to the site of occlusion.

CONCLUSIONS

A case of segmental torsion and necrosis of the left tube occurring in a virgin is herein recorded. The onset was sudden in the early menstrual phase. The left sided pain recurred monthly until admission to the hospital. A twisted tube with two complete turns at the junction of the middle and outer thirds was erroneously interpreted as an ovarian cyst. Pathologically, the dilated portion of the tube was the seat of an old hematoma and the wall was completely necrotic distal

much of the growth as possible. Accordingly, under gas anesthesia, a cautery excision of the growth was performed. During the procedure, all areas where the melanoma had reached the surface, were fulgurated with the electric current. Following the operative procedure, the patient was more comfortable, but continued to lose considerable weight and developed a moderately severe cough. On Feb. 21, 1937, the patient began to develop symptoms of pulmonary congestion and thereafter the course was progressively downward and terminated in death on March 1, 1937.

Autopsy revealed melanoma of the vulva with metastases to inguinal lymph nodes, lungs, stomach, and pancreas. Both lungs were riddled with tumor nodules which varied in size from that of a pea to that of a plum. The metastasis to the stomach consisted of a small, flat, white nodule on the greater curvature. The metastasis to the pancreas was not seen in the gross examination of the organ, but microscopically consisted of a circumscribed mass of tumor tissue in which the cells were spindle shaped. In the lymph nodes, the lymphoid tissue was entirely replaced by tumor, with large areas of hemorrhage and necrosis.

Acknowledgement is here made to Dr. B. Z. Cashman for permission to report this case; to Dr. Mortimer Cohen for the pathological data; and to Miss Ann Shiras for the photographs.

3710 FIFTH AVENUE.

CARCINOMA OF THE CERVIX DURING PREGNANCY*

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CARCINOMA of the cervix, being found so rarely as a complication of pregnancy, especially in women who are pregnant for the first time, prompted us to report this case.

CASE J-6234.—A white patient, E. P., aged 22 years, was admitted to the Gynecological Service of Dr. T. B. Carroll in the Montefiore Hospital on Aug. 27, 1937. She was seen the week prior in the Obstetrical Out-patient Department. Her chief complaint was that one week before admittance to the hospital, she had noticed spotting after coitus for the first time. This bleeding was painless.

For a month or so prior to this, she had noticed a white vaginal nonodorous discharge. Her menstrual history showed nothing irregular. Puberty occurred at sixteen years of age, her periods being regular, every twenty-eight days, lasting five days, and of moderate amount. Her last menstrual period was on Feb. 19, 1937 and of the usual duration. Patient had been married one year and had never been pregnant before. No history of abortions or miscarriages. Her family history showed no evidence of cancer or tuberculosis. Her father and mother, two brothers, and two sisters, are all living and well.

Abdominal examination revealed the abdomen enlarged to the size of about six months' pregnancy. The baby was in R. O. A. position with fetal heart sounds heard in the right lower quadrant.

Vaginal Examination: Attached to the anterior lip of the cervix was a soft, friable, everted, cauliflower, vascular mass, the size of a lemon, attached by a short pedicle. The uterus was not fixed, the fornices were clear, and the tumor with the cervix could be delivered entirely outside of the vagina. At first, one thought of the possibility of malignant degeneration of a cervical polyp.

On Sept. 2, 1937 the patient was operated upon and the mass was removed with its small pedicle with the actual cautery. On Sept. 7, 1937 patient was in excellent condition but said that she felt no fetal movements. Fetal heart sounds could not be heard. On Sept. 9, 1937 patient delivered herself of a macerated fetus, spontaneously, with no complications. On Sept. 20, 1937 patient received a course of

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so packed with pigment that the cell outline was lost. There were areas of necrosis, but for the most part the tumor was quite cellular. With the Wilder silver stain, some of the spindle-shaped cells had fibrils, while other cells were devoid of fibrils. The fibril-free cells predominated. The distribution of the pigment varied in different cells, some of the cells being so packed with pigment as to render obscure the cell outlines, while other cells were devoid of pigment.

Diagnosis: Melanoma of the vulva.



Fig. 1.

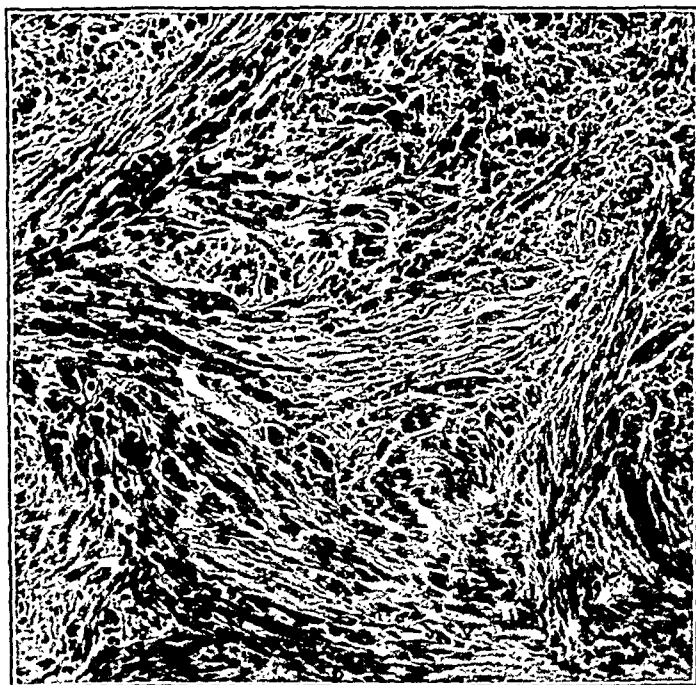


Fig. 2.

Following radiation, the mass seemed to shrink to about two-thirds of its former size and was the seat of a profuse seropurulent exudate, with the patient experiencing considerable discomfort in this area. On Jan. 17, 1937, under nitrous oxide anesthesia, radium needles were again inserted, this time around the periphery of the tumor and allowed to remain in situ for forty-eight hours (2400 mg. hr. of radiation). Symptoms continued practically the same, the patient losing ground very rapidly. On Feb. 10, 1937, about seven weeks after the initial radiation, due to the extreme discomfort of the lesion to the patient, it was decided to excise as

Pathological Report, by Dr. K. Yardumian: Gross Findings: The specimen consisted of a tumor mass, measuring 6 by 5 by 4 cm. with a pedicle. It was cauliflower-like, soft and friable in consistency, pinkish gray in color, showing areas of hemorrhage.

Microscopic Findings: Sections of the tumor showed various pictures in different parts of the tissue. There were areas highly vascular with poorly defined vascular walls with very little stroma. The cells were vacuolated, multiform, with a tendency to form giant cells, while in other parts there were islands of cells with tendency to form acini. Cells were uniform in size, hypochromatic nuclei, and numerous mitotic figures. There were strands of fibroconnective tissue, separating the acini. The general picture of the tumor was that of a very fast growing adenocarcinoma with areas resembling sarcomatous degeneration. However, this might have been due to the rapid course of the tumor.

Diagnosis: Adenocarcinoma of the cervix (embryonic in type).

NOTE: Since this report was submitted, the patient was seen in the clinic on March 11 and April 8, 1938. She had no complaints and was in excellent health, having gained four pounds. Pelvic examination revealed no evidence of metastasis, the cervix was clean and healed, the uterus in anterior position and freely movable, and of normal size and consistency. The parametria were free.

I wish to thank Dr. T. B. Carroll for permission to report this case and for his helpful suggestions in the treatment.

4135 JENKINS ARCADE

TORSION OF THE FALLOPIAN TUBE*

SANFORD KAMINESTER, M.D., F.A.C.S., BROOKLYN, N. Y.

THE present case, in which torsion was produced by a small parovarian cyst, is reported simply to bring to mind the possibility of this condition existing in all cases of obscure intra-abdominal disturbance in the female.

Mrs. L. S., married, white, was seen in consultation on Jan. 11, 1937. She was 24 years of age and had been married for four years. At about the time of her marriage she had been operated upon for appendicitis. She had been pregnant once and had been delivered of an average size child two years after her marriage. One year before the occurrence of the present illness the patient had had an attack of pain in the left lower quadrant which had subsided after twenty-four hours without treatment.

On Jan. 9, 1937, there had been an attack of severe pain over the left lower quadrant associated with vomiting. This pain continued with remissions for two days, at which time hospitalization was advised. The menses had always been regular and the last period had occurred on Dec. 25, 1936.

Examination revealed a well-nourished, well-developed adult female who was suffering intensely. Temperature was 101.4° F., pulse 90, respiration 22, and blood pressure 124/80. Abdominal examination showed a well-healed, right rectus scar and also revealed marked tenderness in the left lower quadrant associated with rebound tenderness. On pelvic examination there was no bleeding. The cervix was in position and very painful on attempted motion. The uterus could not be definitely made out due to the abdominal spasm and tenderness. In the left fornix there was a very tender, irregularly shaped mass.

The urine was normal. Blood examination showed 9,750 white blood cells, with 72 per cent polymorphonuclear leucocytes.

A preoperative diagnosis of torsion of an ovarian cyst or hemorrhage from a ruptured follicle was made and laparotomy decided upon.

*Presented at a meeting of the Brooklyn Gynecological Society, March 4, 1938.

deep x-ray therapy. She was instructed to return in a month for radium treatment. The patient, however, was noncooperative and, in spite of urging by the social worker, did not return until Dec. 21, 1937. She was then given 3,600 mg.

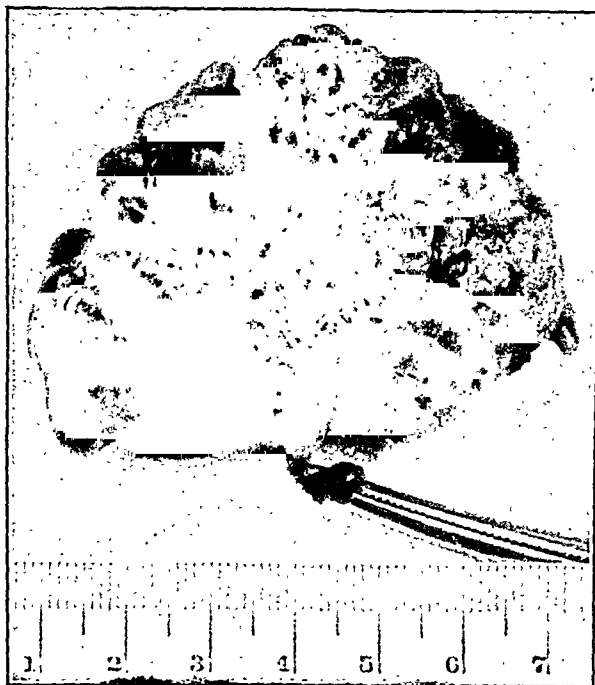


Fig. 1.—Cauliflower-like tumor mass, measuring 6 by 5 by 4 cm. with a pedicle, removed with the cautery.

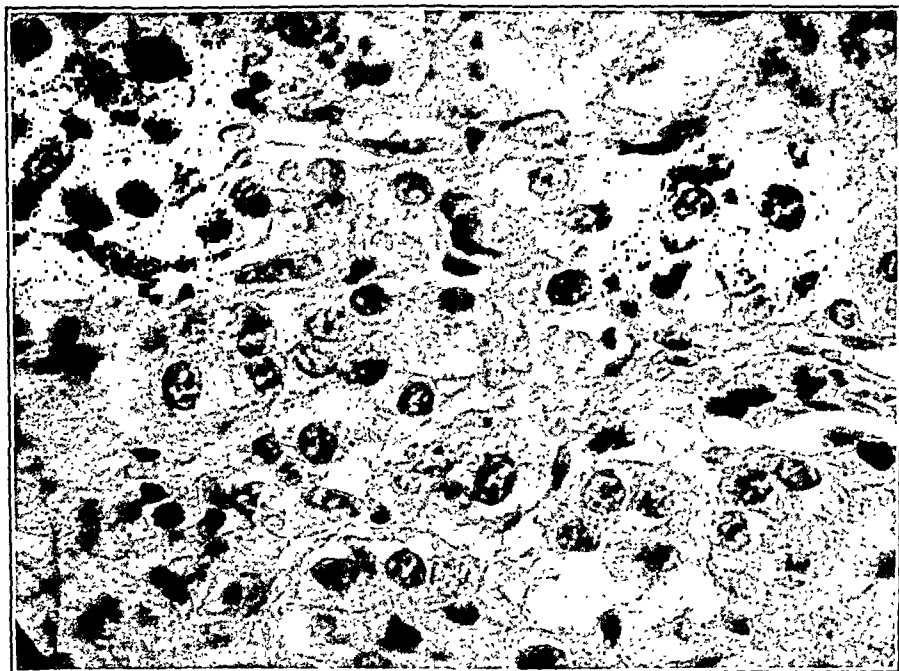


Fig. 2.—High Power 400X H. E. Showing large undifferentiated epithelial cells, hyperchromatic nuclei, few mitoses, vacuolated cytoplasm.

hr. of radium. Examination at that time revealed the cervix healed, uterus in anterior position, normal size, and freely movable, with the fornices clear. The blood count was within normal limits, urethral smear was negative for gonococci. The blood Wassermann was negative.

ATRESIA OF THE VAGINA*

JOSEPH L. BAER, M.D., CHICAGO, ILL.

THE following case report deals with a complete atresia of the upper two-thirds of the vagina, i.e., that portion of the vaginal tube which arises from the fusion of the lowermost parts of the Müllerian bodies.

The patient, E. M., aged 16 years, had never menstruated. Her identical twin sister had menstruated more or less normally for approximately two years. The girl was seen by the school physician who found a mass in the abdomen. She was then brought to me. On examination the external genitalia were normal. It was possible to insert the first phalanx past the intact hymen into a closed pouch, the depth of which was no greater than 2 cm. On rectoabdominal examination the mass which the school physician had felt was about the size of a four months'

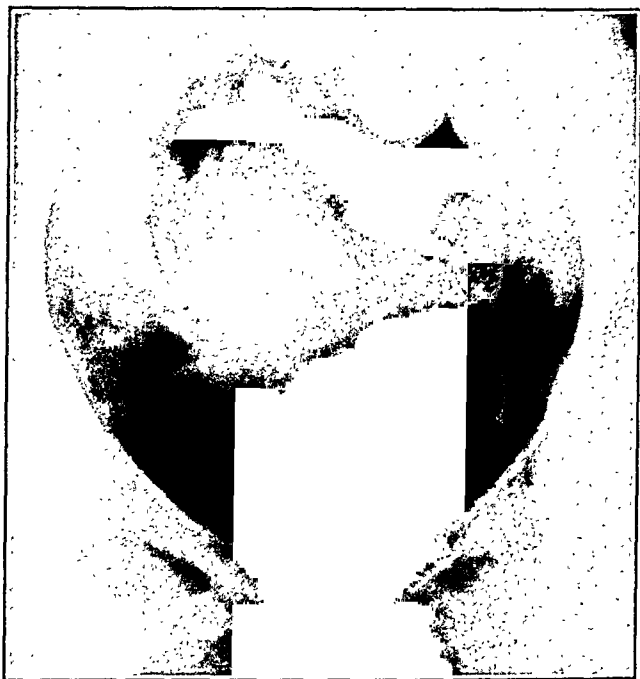


Fig. 1.—Pelvic roentgenogram by transabdominal pneumoperitoneum showing uterine mass with a more opaque core (hematometra).

pregnancy, with something of the outline of the uterus, freely movable, insensitive and with a tapering lower pole. An intravenous pyelogram was made to make sure there was no anomaly of the urinary system, and then a transabdominal pelvic roentgenogram was made, in order to determine the amount of tissue that lay between the lower pole of the mass and the apex of the exceedingly small vaginal tube. The approximate distance between this tiny vaginal vault and the lowermost pole of the uterine mass was 6 cm. Evidently only the ectodermal invagination had taken place. The denser shadow within the uterine mass was interpreted as retained menstrual blood.

There are two surgical approaches to this problem, one, vaginal, the other abdominal. In the literature two points are emphasized; first, that if possible, where there is functioning endometrium it is desirable to establish menstruation by connecting the blind lower uterine pole with the vaginal pouch; second, in the adolescent

*Presented at a meeting of the Chicago Gynecological Society, December 17, 1937.

Under spinal anesthesia, the abdominal cavity was opened. The left tube was found in the cul-de-sac. It was freely movable and could easily be delivered into the wound. The distal half of the tube was swollen and hemorrhagic and almost black in color. It had twisted 180 degrees, this twist being produced by a small cystic tumor which was attached to the mesosalpinx by a fibrous band. The ovary was not involved. The right tube and ovary appeared normal. The left tube and ovary were removed, care being taken to transect through normal tissue to avoid the possibility of cutting through thrombosed vessels. Convalescence was uneventful.

Examination of the removed specimen showed the tube to be 9 cm. in length, 2 cm. in diameter at its fimbriated end and 4 mm. at the proximal end. The outer

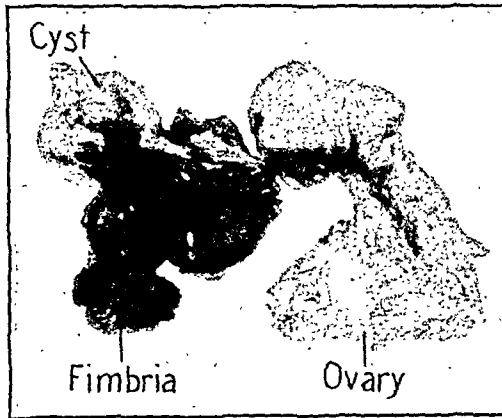


Fig. 1.—Showing torsion of tube due to ovarian cyst.

half was deeply hemorrhagic and swollen, although the fimbria were still distinct and the abdominal ostium patent. Attached to the mesosalpinx was a cystic structure measuring 2 by 3 cm. in diameter. This structure had caused beginning necrosis of the tube by strangulating it at its mid-portion. The wall of the cyst measured 3 mm. in thickness and was infiltrated with blood. The ovary, which measured 3 cm. in diameter, was normal on gross and microscopic study. The proximal part of the tube showed edema and some infiltration of the wall with polymorphonuclear leucocytes. The distal portion and the wall of the cyst were so hemorrhagic that no further detail could be made out.

340 ST. JOHNS PLACE

A CASE OF SECONDARY ABDOMINAL PREGNANCY*

CRAIG WRIGHT MUCKLE, M.D., PHILADELPHIA, PA.

(From the Philadelphia Lying-In Hospital)

THE value of the diagnostic methods utilized in the following case of abdominal pregnancy seems to warrant its presentation.

M. M., a 25-year-old negress, was admitted to the Pennsylvania Hospital on May 22, 1937. Menstruation began at the age of thirteen years, occurred regularly every twenty-eight days, lasting three and a half days and was accompanied by cramps at the onset. She was married in June, 1933; was delivered of one child by breech extraction in October, 1936. The last menstrual period prior to admission began on Dec. 2, 1936 and lasted three days.

From the middle of December, until her admission, she had been more or less constantly troubled by distention, gaseous eructation, and constipation.

On Jan. 17, 1937 she was admitted to another hospital for six days because of vomiting, obstipation, and swelling of the abdomen. She improved rapidly under conservative treatment and was discharged with the diagnosis of autointoxication.

On May 9, 1937 vaginal bleeding began and the following day the patient passed a piece of tissue three inches long which she said "looked like a dog's tail." Slight vaginal bleeding continued for a period of ten days. She was admitted to the hospital on May 22 because of abdominal distention, vomiting, and constipation. The temperature was 99.2° F.; pulse and respirations, normal. The abdomen was tense, swollen, and signs of free peritoneal fluid were present. The abdominal enlargement was symmetrical and a mass was felt extending from the symphysis to a point one fingerbreadth below the umbilicus. There was moderate tenderness but no rigidity. On examination the vaginal mucosa and cervix were soft and cyanotic. No adnexal masses were felt. There was no vaginal bleeding. The blood count was 2,900,000 red cells; 6,800 white cells, hemoglobin 8 gm.; the differential count was normal.

On admission the tentative diagnoses were intrauterine pregnancy of five months' duration or hydatidiform mole.

The Friedman test was positive but a quantitative determination revealed no excess of prolan.

The piece of tissue which had been passed spontaneously was examined by Dr. Robert F. Norris, who submitted the following report:

"The tissue in formalin was cylindrical and measured 6 cm. by 2 cm. It was reddish brown in color with a rough granular surface. Grossly it appeared to be a cast of necrotic tissue from the uterine cavity. Microscopically the tissue was somewhat autolyzed and consisted entirely of decidual cells with pink cytoplasm and large dark staining nuclei which appeared normal. There was no variation in the size, shape, or staining qualities of the cells. No chorionic villi were seen. The presence of decidual tissue without chorionic villi suggests the possibility of an extrauterine pregnancy. *Diagnosis:* Decidual cast from uterine cavity."

The history of amenorrhea and the size of the abdominal tumor indicated pregnancy. This was confirmed by a positive Friedman test. Abdominal distention and pain constituted the chief complaints. The absence of chorionic villi in the decidual cast suggested extrauterine pregnancy.

On x-ray examination, Dr. Paul Bishop submitted the following report:

"There is a single fetus lying transversely across the upper abdomen, the head to the maternal left side, the buttocks to the right. The stomach is displaced upward, the transverse colon downward and the fetus does not seem to be connected with the uterus." In conference, Bishop pointed out that a loop of intestine was lying *below* the fetus instead of being displaced upward by the growing uterus.

To clarify the diagnosis, an x-ray study was made after intrauterine injection of iodized oil:

"On the injection of lipiodol the uterus is found to be slightly larger than the average nongravid uterus and tilted toward the left side. The fetus is found to

*Read at a meeting of the Obstetrical Society of Philadelphia, January 6, 1938.

girl it is highly desirable to do nothing more, but to await marriage. If the tiny vaginal tube remains inadequate for coitus and it becomes necessary to do a vaginal plastic operation, then marital coitus is essential to the permanent success of the plastic operation. So in this instance the vaginal approach was selected.

Under ethylene-oxygen anesthesia the apex of this tiny vaginal vault was split transversely, and then with a sound in the urethra and bladder and the assistant's finger in the rectum, we proceeded with blunt and sharp dissection through the rectovaginal tissue. Meanwhile abdominal pressure was made to bring the lower pole of the mass somewhat closer to the cul-de-sac. Eventually it was possible to grasp the lower pole with a tenaculum, and then with a little further blunt dissection a single droplet of black, thick fluid appeared, obviously some retained menstrual blood. With sound exploration the canal of the cervix was identified and dilated.



Fig. 2.—Same plus visualization of hypoplastic vaginal pouch distended by opaque medium. Note the distance between the vaginal vault and the uterine mass.

Approximately 10 to 12 ounces of retained black menstrual blood escaped. The so-called cervix was then brought down to the level of the little vaginal vault where it was anchored with mattress sutures. The girl made an uneventful convalescence. The date of the operation was October 16 and last week, December 10, she had her first normal menstrual period.

The abdominal approach in these patients is distinctly unsatisfactory. The depth of the cul-de-sac and the dissection necessary to reach such a tiny vaginal pouch from above is obviously more difficult than the approach from below. However, if the all-important preliminary intravenous pyelogram reveals possible involvement of one or both ureters in the anomalous development, then the abdominal approach becomes the safer route.

Special Article

THE INTRAVENOUS ADMINISTRATION OF POSTPITUITARY EXTRACT FOR OBSTETRIC PURPOSES

A NOTE ON THE TWENTY-FIFTH ANNIVERSARY OF THE INTRODUCTION OF
THIS PROCEDURE

J. HOFBAUER, M.D., CINCINNATI, OHIO

“Finality is rarely attained in any field of human interest.”

—LaFayette B. Mendel.

THERE is perfect unanimity regarding the unique merit of post-pituitary extract both for the initiation and stimulation of regular intermittent uterine contractions at term and during labor. While in the past the drug has been almost exclusively employed by subcutaneous injection, increased interest is being evidenced in recent years in its intravenous administration. It is my purpose in this communication to give a comprehensive review of the indications and contraindications of the use of this method for various obstetric conditions, as established by actual experience and also to correct certain recent misrepresentations.

In 1912, now twenty-six-years ago, the present writer advocated the intravenous administration of pituitary extract “when during labor an immediate and prompt response is essential.”¹ In a more extended paper, the indications for this new method were discussed and a dose of two or three minims of the commercial preparation, routinely *diluted* with 1 c.c. of normal saline solution and to be injected slowly, was recommended.²

Abortion.—While in one of his early publications on the subject, the author emphasized that, for the induction of abortion pituitary extract is of no avail, its intravenous administration preceding intrauterine manipulations for emptying the uterine cavity, was found highly satisfactory. The fact that the wall of the pregnant uterus contracts rigidly in response to its intravenous injection, renders any attempt to remove the remnants of the product of conception instrumentally, easier and less risky, especially in less trained hands. In preference to the intravenous administration by an assistant, I, as a routine for the past few years, inject an ampoule of obstetric pituitrin *into the substance of the posterior lip of the uterine cervix* with uniformly satisfactory results. Vigorous spastic contractions of the uterine muscle ensues almost immediately. In our series of observations it was worthy of note that the wall of the uterine cervix remained unaffected, while the musculature of the fundus immediately responded to the intracervical injection of pituitrin. These clinical observations of the insensitivity of the uterine cervix to pituitary extract have, of late, been fully confirmed by Newton in experiments on laboratory animals.³

Induction of Labor.—While the oxytocic principle of the posterior pituitary lobe when given *in small doses* subcutaneously, renders valuable service for the induction of labor at term,² the intravenous administration of the drug for such purposes is to be deprecated on account of the not infrequent occurrence of tetanic contractions of the uterus, which

be definitely outside the uterine cavity. No lipiodol has extended outward into the tubes."

Laparotomy was performed on May 27, 1937. The amniotic sac was adherent to the transverse colon. A stillborn, unmacerated fetus was removed. The placenta lay in a rent in the right Fallopian tube. The left tube and both ovaries were normal. The uterus was slightly enlarged. A supravaginal hysterectomy and right salpingectomy were performed. Maternal convalescence was uneventful.

SUMMARY

1. The patient was admitted because of abdominal pain and history of five months amenorrhea followed by vaginal bleeding.
2. The Friedman test was positive.
3. There were decidual cells present without chorionic villi.
4. Roentgenogram showed the fetus high in the abdomen.
5. Uterosalingogram revealed the uterus only slightly enlarged and displaced downward and to the left.

CONCLUSION

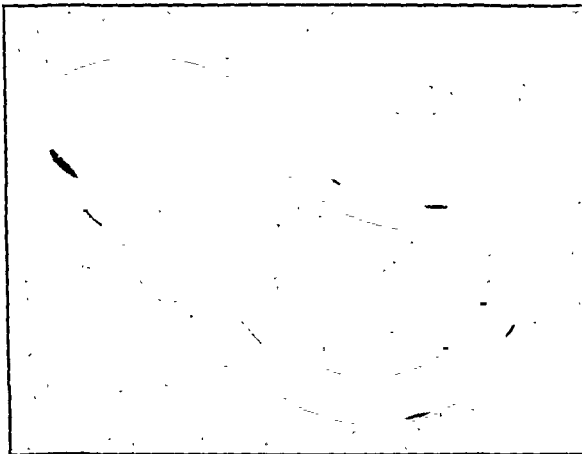
Examination of tissue from the uterine cavity for the presence of chorionic villi, and uterosalingography are two valuable aids in the diagnosis of abdominal pregnancy.

A PESSARY FOR MODERATELY-SIZED CYSTOCELES

CHENEY M. STIMSON, M.D., PHILADELPHIA, PA.

(From the Department of Gynecology, Jefferson Medical College)

THE illustration represents a modified Smith pessary, designed for the support of moderately-sized cystoceles. The modification differs from the regular Smith retro-displacement pessary, in that the smaller end, that which rests against the anterior vaginal wall, affords a solid surface, against which the cystocele may press. The vacancy, formerly enclosed at the smaller end of the pessary, is filled in with hard



rubber, the same as that used in the rest of the pessary. There should be left at the larger end, the lumen, sufficient room for the cervix, and for the bar to slip in place in the posterior fornix.

I have used sizes 0, 1, and 2, for moderately-sized cystoceles, where there was fairly good perineal support. In such cases this pessary proved quite satisfactory. But for the reason that perineal support is usually lacking in larger cystoceles, I have not tried larger sizes.

generalized convulsions may occur in this group of patients following the exhibition of postpituitary preparations.¹⁰ Schockaert recently observed severe convulsions in three pre-eclamptic women, following the administration of a few minims of postpituitary extract.¹³ In this conjunction, attention is called to my recent analysis of the hormonal aspect of the pathogenesis of eclampsia.¹¹

Cesarean Section.—Immediately after the delivery of the baby by cesarean section, I have routinely injected solution of pituitary into the cubital vein. The uterus blanches and remains firmly contracted. This procedure distinctly facilitates the insertion of sutures into the uterine wall. We feel that this method is in several respects superior to the intramural injection of postpituitary. Ergot is administered hypodermically as an efficient adjunct and safeguard, ten minutes after the intravenous administration of pituitary extract.

Anesthesia and Analgesia.—Anesthetics and analgesics (chloroform, ether, pantopon, morphine, chloral) in no way impair the effect of solution of postpituitary during labor.² In 1928, the rectal administration of amytal was introduced. Our observations of rapid cervical dilatation, considerable alleviation of pain, amnesia, regularity of uterine contractions have been confirmed by several investigators. The evidence now at hand shows that the postpituitary oxytocic effect is not abolished in the parturient woman by amytal or nembutal twilight sleep.

Placenta Previa.—Ante-partum bleeding in cases of low implantation of the placenta and of placenta marginalis may be controlled, in most instances, by the artificial rupture of the membranes combined with the subcutaneous administration of a minute amount of postpituitary. The resulting uterine activity presses the presenting vertex against the detached placental margin and uterine wall and thus controls bleeding.² The intravenous use of a solution of pituitary for placenta previa, a procedure suggested by Sachs, warrants severe criticism.

Post-partum Atony.—No dissenting voice has ever been raised against the invaluable aid rendered the obstetrician by the intravenous exhibition of postpituitary extract in the treatment of post-partum atony. The consensus of opinion prevails that this method which was advocated by the writer in 1918, has saved the life of the parturient woman on innumerable occasions. For the successful treatment of uterine atony post partum, the intravenous injection of a solution of pituitary deserves special consideration. "I believe it to be the greatest asset to the security of the doctor and the safety of his patient that has been given us in years" (Alden, Jackson). With this method, a dramatic, immediate and sustained response is obtained, the uterus contracting vigorously and remaining firm. For many years, I have followed the intravenous administration of postpituitary with neo-ergotamine, and I have never been obliged to pack the uterine cavity. The same method is employed after replacement of the inverted uterus.

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may persist for several minutes and seriously endanger the fetus. The nasal route, on the other hand, represents an appropriate procedure for the induction of labor in both normal and complicated cases.

Pyelitis.—Diminution of tone of the musculature of the ureter and ureteral dilatation were described by the author, in 1928, as constant concomitants of normal gestation. Impairment of the expulsive forces of the ureter in the gravid state, with the atony even more marked in the presence of superimposed urinary infection, was stressed as a definite impediment to the free discharge of urine, thus enhancing the risk of infection of the urinary tract and reducing its capacity to eliminate an actual bacterial infection.⁴

New efforts of therapeutics were based upon the observation in man and in animal experiments that the musculature of both the renal pelvis and ureter respond with peristaltic movements to pituitary extract.⁴ This drug was found to act even more definitely in the presence of considerable atony of the structures. The inference was obvious. Augmenting the tone and peristalsis of the ureter and, thus, accelerating the drainage of the atonic ureter in cases of pyelitis, appeared a rational procedure. The exhibition of solution of pituitary, and recently of pitressin, has proved useful in this respect. Our observations have been substantiated by Reiman,⁵ Jona and Flecker,⁶ DeLee,⁷ Stoeckel,⁸ Draper,⁹ Lower and Naujoks. Striking relief of pain, associated with objective improvement, and diminution of the abnormal elements in the urine, were apparent in the overwhelming majority of cases of pyelitis thus treated. Recently, we have combined with this treatment the oral administration of prontosil. In obstinate cases, when the subcutaneous injection of pitressin fails to remedy the situation, the intravenous route of administration has proved superior. Success was noted with this treatment in every case of pyelitis observed during the puerperium. Our experience demonstrates that in most instances of pyelitis in pregnancy ureteral catheterization can advantageously be obviated by the exhibition of a solution of post-pituitary, if combined with prontosil. For those rare cases which are not benefited by this method and require instrumental drainage, pituitary therapy as an additional measure, has proved of distinct advantage. Even after normal pregnancy, when during its course an undue number of leucocytes has been repeatedly observed, the exhibition of pituitary by the hypodermic or intravenous route, with a view to restoring the dynamics of the ureter to normal, is well grounded in actual practice.

Labor.—With the indications for the use of postpituitary extract during labor, I do not propose to deal in detail. The statement made in our first communications on the subject, that uterine inertia represents its principal indication, has withstood the test of time and progress.

Repeatedly we have warned that pituitary extract is out of place in the presence of cervical obstruction, overstretched lower uterine segment, manifest disproportion, rigid perineum; and also, that misapprehension of the obstetric situation and indiscreet dosage invite calamity. In other words, the use of this potent remedy should be tempered with judgment, proper regard for indication and dosage being most essential.

In my hands, the intravenous administration of one minim of solution of pituitary has proved serviceable during labor in cases which did not respond to the subcutaneous hypodermic administration of the drug.

Eclampsia.—The heightened response of the pre-eclamptic and eclamptic woman to posterior pituitary extract constitutes a contraindication to its employment. As observed in the previous paper on the subject,

There are many pitfalls and variables to be considered, therefore the question of dosage always demands thought and consideration.

In the treatment of gonorrheal vaginitis of children as advised by Lewis¹ 1,000 I.U. by vaginal suppository are given daily until the discharge becomes acid and gonococci disappear (total dosage 30-50,000 I.U.).

In the treatment of the menopause marked divergence of opinion exists. In a series of cases controlled by hormone assay and vaginal spreads² an average of 150,000 I.U. per month were required. The estrogens were found equally effective whether given by injection or by mouth, although larger dosage is required. Werner³ obtained relief of symptoms with as little as 5,000 I.U. total (500 I.U. every third day for ten doses) injected in oily medium. All agree that repeated courses of treatment are required at intervals as the symptoms recur. Uterine bleeding may follow when medication is stopped. This form of treatment relieves not only the flushes and sweats but also psychological, arthritic, digestive and local vaginitic symptoms temporarily.

To produce bleeding in amenorrhea a much larger dosage is required.⁴ Bleeding may result from one million I.U.; frequently triple this amount is needed. The periodic return of menstruation by means of estrogens still remains a doubtful procedure, many careful observers having denied its success.

Estrogens have been used empirically for the treatment of numerous other conditions among which are hirsutes, toxemia of pregnancy, frigidity, sterility, dysmenorrhea, acne, etc. Theoretically such application appears illogical; the published reports are uncritical; no attempt to standardize dosage can be made for these conditions.

In prescribing and using estrogens the physician must select the preparation to be given according to the special requirements of the patient, keeping in mind the potency (I.U.), the vehicle, and the rate of absorption and excretion.

¹Lewis, R. M., and Adler, E. L.: J. A. M. A. 106: 2054, 1936.

²Frank, R. T., Goldberger, M. A., and Salmon, U. J.: N. Y. State J. Med. 36: 1363, 1936.

³Werner, A. A., Jones, G., Roberts, J., Brown, G. O., Neilson, C. H., and Rothermich, N. O.: J. A. M. A. 109: 1027, 1937.

⁴Frank, R. T., Goldberger, M. A., Salmon, U. J., and Felshin, G.: J. A. M. A. 109: 1863, 1937.

Editorial

The Dosage of the Estrogens

THE increasing employment of sex hormones in the treatment of gynecologic and other diseases calls for definite and accurate knowledge of the indications for their use and above all, of their dosage. While brilliant results are claimed for them as substitutes after operative or radiation treatment, much confusion has arisen from the many trade names under which estrogenic compounds are dispensed. Refinements in manufacture have made some of them available in crystalline form, synthetically produced, particularly the estrogens which are commonly known as estrone (theelin, ketohydroxyestrin, etc.) or estradiol (theelol, dihydroxyestrin, etc.).

Their satisfactory clinical application depends largely on proper and adequate dosage.

The estrogens, one of the two female sex hormones, the other being progesterone, the nidatory corpus luteum hormone, are now available in pure crystalline form. The estrogens are used clinically mainly in the form of estrone (theelin, ketohydroxyestrin) or estradiol (theelol, dihydroxyestrin). Confusion arises from the many trade names under which estrogenic compounds are disguised, amniotin, theelin, progynon-B and DH, ago and sistomensin, emmenin, menformon, to mention only a few. An international unit evaluating the potency of any given preparation of estrogens has been accepted. It is the effect produced by 0.1 *gamma* ($\frac{1}{10,000}$ of a gram) of estrone (theelin). This roughly corresponds to a mouse unit or $\frac{1}{5}$ to $\frac{1}{4}$ of a rat unit. For uniformity's sake all preparations should be standardized to the *international unit* (I.U.).

Some of the preparations are dispensed in water soluble, other in lipid soluble form. The rate of absorption, continuity of action and consequent physiologic effect produced is profoundly influenced both by the vehicle used and the site of injection.

Water soluble preparations are both more rapidly absorbed and excreted. Consequently more frequent injections and larger dosage is required. Oily solutions are taken up more slowly. The rate of absorption is more rapid from muscle than subcutaneous tissues. The disadvantage arising from repeated oil injections are the possible formation of painful, long persisting indurations or granulomas. Several preparations can be given by mouth. This is preferable to the patient but does not permit of as accurate dosage as by the parenteral route, because the amount of absorption through the intestinal tract varies in different individuals and under different conditions of food intake and intestinal function. Absorption of estrogens through the vaginal mucosa and through the skin likewise occurs. This method should not be used over long periods of time because carcinogenic potentialities are increased by topical application.

MEETING OF DECEMBER 17, 1937

The following papers were presented:

Studies in the Evaluation of Mammography. Dr. Ralph A. Reis.

Infant Mortality at the Cook County Hospital Among 16,000 Deliveries. Drs. David S. Hillis and S. J. Benensohn. (By invitation.) (For original article, see page 427.)

The Pathologic Properties of Meconium. Drs. Wm. H. Rubovits, E. Taft (by invitation) and F. Neuwelt (by invitation). (For original article, see page 501.)

Effect of Placental Extract on Endometriosis. Dr. Mark T. Goldstine.

Atresia of the Vagina. Dr. Jos. L. Baer. (For original article, see page 518.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF MARCH 4, 1938

The following papers and case reports were presented:

Segmental Torsion of Fallopian Tube in a Young Virgin. Drs. Samuel A. Wolfe and David Kuperstein. (For original article, see page 509.)

Torsion of the Fallopian Tube. Dr. S. Kaminester. (For original article, see page 516.)

Primary Uterine Inertia. Dr. William S. Smith.

The Problem of Infant Mortality. Dr. Joshua Ronsheim. (For original article, see page 419.)

WASHINGTON GYNECOLOGICAL SOCIETY

MEETING OF JANUARY 23, 1937

The following paper was presented:

The Use of Para Amino Benzene Sulphonamide or Its Derivatives in the Treatment of Beta Haemolytic Streptococcal Infections. Dr. Perrin H. Long and Eleanor A. Bliss.

MEETING OF MARCH 27, 1937

The following papers were presented:

Treatment of Gonorrheal Vulvovaginitis With Corbus-Ferry Filtrate. Dr. D. H. Kushner.

Diabetes Insipidus Complicated by Pregnancy. Dr. Herman Hertzberg.

Tumors of the Ovary. Dr. William Neill.

MEETING OF OCTOBER 23, 1937

The following papers were presented:

Neurotic Excoriations in Pregnancy. Dr. Edward M. Ellerson.

Impetigo Herpetiformis. Dr. I. Lewis Sandler.

OBSTETRICAL SOCIETY OF BOSTON

MEETING OF NOVEMBER 16, 1937

The following paper was presented:

Obstetric Analgesia and Anesthesia. Dr. Charles P. Sheldon.

PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 7, 1938

The following papers were presented:

Carcinoma of the Cervix During Pregnancy. Dr. Samuel Goldstein. (For original article, see page 514.)

Melanoma of the Vulva. Dr. R. C. Nucci. (For original article, see page 512.)

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF NOVEMBER 9, 1937

The following paper was presented:

A Contribution to the History of Obstetrics in New York City. Dr. Claude E. Heaton.

MEETING OF DECEMBER 14, 1937

The following papers were presented:

The Effect of Pregnancy on Women With Rheumatic Heart Disease. Dr. Burton K. Hamilton (by invitation).

Heart Disease Complicating Pregnancy. Dr. H. J. Stander. (For original article, see page 413.)

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF NOVEMBER 4, 1937

The following paper was presented:

Fetal Respiration in Relation to Atelectasis and Intrauterine Pneumonia. Drs. Franklin F. Snyder and M. Rosenfeld. (For original article, see page 363.)

MEETING OF DECEMBER 2, 1937

The following papers were presented:

The Prenatal Management of Breech Presentation. Dr. Jos. V. Missett.

The Management of Breech Deliveries. Dr. Roy W. Mohler. (For original article, see page 400.)

MEETING OF JANUARY 6, 1938

The following papers were presented:

A Case of Secondary Abdominal Pregnancy. Dr. C. W. Muckle. (For original article, see page 520.)

The Safety and Advantages of Office Curettage. Drs. S. Leon Israel and Charles Mazer. (For original article, see page 445.)

An Evaluation of the Sedimentation Test in the Differential Diagnosis of Acute Pelvic Inflammatory Disease and Acute Appendicitis. Drs. Charles Lintgen and Kenneth Fry. (For original article, see page 393.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF OCTOBER 22, 1937

The following paper was presented:

Inversion of the Uterus. Dr. Franklin E. Hall.

Hyperemesis Gravidarum. Drs. J. E. Fitzgerald and A. Webster. (For original article, see page 460.)

MEETING OF NOVEMBER 19, 1937

The following papers were presented:

Complications of Radiation Therapy in Cancer of the Cervix. Dr. Max Cutler.

Clinical Manifestation of Stricture of the Ureter in Women. Drs. E. L. Cornell and D. F. Rudnick.

by the thyrotropic hormone are strikingly similar to those of exophthalmic goiter in man, Marine speculated on the possibility that exophthalmic goiter occurs when the capacity to produce antihormone is impaired. Van Coubert and Stahl showed that thyroxin to a certain extent antagonizes the physiologic activity of the anterior lobe of the pituitary, and Kuschinsky demonstrated that the thyrotropic hormone content of the pituitary gland is inversely proportional to the thyroxin output of the thyroid gland.

For centuries it has been known that an increase in the size of the thyroid gland may occur during the menses and pregnancy and at the time of puberty and the menopause. Within comparatively recent years it has been noted that either hyperthyroidism or hypothyroidism may be accompanied by disturbances of menstruation, a decrease of fertility, and abortion. Marine stated that complete castration of dogs and rats is usually followed by a decrease in the size of the thyroid gland and a lowered rate of metabolism. Van Horn found that moderate thyroid feeding helps to eliminate estrin, although at the same time it stimulates the gonadotropic hormone of the anterior lobe of the pituitary to an increased production of estrin. Three times as much estrin was required to induce estrus in rats fed thyroid substance as in rats not so fed. It cannot be assumed, however, that these clinical observations or experimental findings are due to any selective action of the thyroid secretion on the ovaries or of the ovaries on the thyroid gland. In all probability the effects are produced through the anterior pituitary lobe, which acts as an intermediary. Evidence to support this belief is found in the temporary increase of gonadotropic and other activities of the pituitary gland following thyroidectomy and the decrease of thyrotropic as well as gonadotropic activity after injection of large doses of estrogenic substance. However, the work of Fluhmann suggests that thyroid substance inhibits the effect on the ovaries of the gonad-stimulating hormone of the anterior pituitary lobe and that this inhibition is the result of the direct effect on the ovary and not the result of indirect action through the anterior pituitary lobe.

Mention has been made that the secretion of the thyroid gland stimulates the body cells to produce energy and heat by regulating the rate of oxygen consumption. The normal average rate of metabolism of the body, calculated according to the DuBois standard, has been arbitrarily placed at zero, with normal variations between 10 per cent above and 10 per cent below this figure. The state of pregnancy demands increased secretion of the thyroid gland. Sandiford and Wheeler found that this was due to the increasing mass of active protoplasmic tissue, consisting largely of the fetal tissues and partly of an increase in maternal structures incident to pregnancy. These authors found that during the early months of pregnancy, there was little if any increase in the basal metabolic rate, but that there was a distinct increase to +20 or +25 per cent from the sixth month to the end of pregnancy. In 1931, Anselmino and Hoffmann demonstrated in the blood of pregnant women a substance which had the properties of thyroxin. This substance reached a maximal concentration at term and was found only in small amounts on the sixth day post partum. Mussey, Plummer and Boothby found that a basal metabolic rate of +25 or +30 per cent was not necessarily an indication of hyperthyroidism in the later months of pregnancy. Plass and Yoakam stated that the total increase of

Department of Practical Problems in Obstetrics and Gynecology

CONDUCTED BY WILLIAM J. DIECKMANN, M.D.

THE THYROID GLAND AND PREGNANCY*

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(From the Section on Obstetrics and Gynecology, Mayo Clinic.)

THE physiologic effect of pregnancy on the thyroid gland and the results of disorders of the thyroid gland on menstruation and the reproductive function have been the subject of considerable investigation and comment. This paper is a review of the more notable articles on these subjects which have appeared in the literature since about 1932. Mention is necessarily made of certain previous observations which clarify more recent statements.

There is an interrelationship of activity of the various endocrine glands. The function of the thyroid gland is the production of a secretion which activates heat and energy production by regulating the rate of oxidation in the cells throughout the body. The anterior lobe of the pituitary gland is the motor activator or dictator of activity of the endocrine glands but certain of its selective activities are held in check by at least some of these glands. For example, prolactin regulates the ovarian secretion of estrin and progesterin, but estrin in turn has an inhibitory action on the production of prolactin by the anterior lobe of the pituitary. Smith and others have demonstrated that removal of the pituitary glands of rats was followed by marked involution of the thyroid gland. These thyroid glands were restored to normal by the injection of fresh anterior pituitary substance. These and other experiments proved that the anterior lobe of the pituitary produces a secretion that stimulates and sustains the thyroid. This fraction of the secretion of the anterior pituitary lobe, the thyrotropic hormone, was isolated by Loeser in 1931 and by Anderson and Collip in 1933; the latter showed that this fraction acted on the thyroid and not on the sex glands. The thyrotropic hormone stimulates the activity of the thyroid cells to hyperplasia and the production of thyroxine and causes the release of stored colloid; too prolonged stimulation produces hyperthyroidism or thyrotoxicosis. Blum, however, observed that the metabolism stimulating effect of the daily administration of this thyrotropic hormone to rats and other animals was not sustained; after thirty to forty days the excessive rate of metabolism subsided, although the thyroid gland still showed hyperplasia. Later Collip and Anderson showed that the resistance to thyrotropic hormone was not due to a thyroid defense mechanism but to a substance circulating in the serum of the thyrotropic-resistant rat. Inasmuch as symptoms produced in animals

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tion is usually hyperactive in this condition. Our observations at the clinic would indicate that patients with hyperemesis may have either an increased or lowered basal metabolic rate, but this is only an occasional finding.

Many women with a basal metabolic rate below the average level do not have symptoms attributable to the hypothyroid state. When symptoms are produced by hypothyroidism, the rate of metabolism can be elevated carefully by the daily oral administration of thyroid extract. Mussey and Haines have advised giving a standard brand of desiccated thyroid in doses of about 4 gr. (0.24 gm.) daily for three or four days and then dropping the dose to from 1 or 2 gr. (0.065 or 0.12 gm.) daily. Determinations of the basal metabolic rate should be made every four to seven days in order to regulate the dosage. The optimal level of metabolism for these patients seems to be from -5 to -8 per cent. After the dose is regulated, determinations of the basal metabolic rate may be made at intervals of weeks or months. The most important observation made by those who have estimated the metabolic rate of many pregnant women may well be the apparent connection between maternal hypothyroidism and fetal anomalies. A pregnant woman with known hypothyroidism should be given enough thyroid extract to raise her metabolic rate to within normal limits. In many instances the metabolic rate will not show the usual rise during the third trimester of pregnancy. In fact we have noted symptoms of hyperthyroidism in a hypothyroid pregnant woman whose basal metabolic rate was elevated to +6 by the use of desiccated thyroid. In cases of hypothyroidism, Davis quite properly urged the institution early in pregnancy of thyroid medication; in fact, in recognized cases it should be begun prior to pregnancy in order that possible abortions or maldevelopments of the fetus may be avoided.

Mention has previously been made of the interrelationship of certain functions of the anterior lobe of the pituitary and of the thyroid and sex glands. The brief account of these functions has a bearing on recent new data concerning the relationship of these three glands during pregnancy. On the basis of this interrelationship Wiegand postulated an interesting theory of the etiology of eclampsia. Proof has been given of the presence in the blood of an antithyrotropic hormone. Wiegand stated that Herold had shown that, in the presence of increased thyroid function, such as in hyperthyroidism or during pregnancy, there is a decrease of antithyrotropic substances. After Eufinger and Anselmino and Hoffmann had found excessive function of the thyroid gland in eclampsia, Wiegand decided to examine the blood of healthy pregnant women and of women with eclampsia in order to determine, if possible, the relative presence of the antithyrotropic substance. After completing these examinations he stated that it was clear that the blood of women with eclampsia had a decreased amount of antithyrotropic substance and that this indicated in these patients an increased function of the thyroid gland which exceeded that of normal pregnancy.

In contrast with this evidence of hyperfunction of the thyroid gland it is of interest to note that Küstner reported administration of thyroxin in certain cases of eclampsia and pre-eclampsia associated with marked edema and albuminuria. Breipohl commented on the work of Küstner and cited the failure of response in similar cases in which patients were treated with thyroid under his supervision.

metabolism due to the rapid rate of metabolic processes in the fetal tissues is about 15 per cent. They accepted the opinion of Benedict that the prediction standards of metabolism are 5 per cent too high for normal women and stated that any rate above +20 per cent was potentially abnormal. Bloss made basal metabolic tests a routine part of prenatal care and concluded that a rate of more than +20 per cent indicated a condition of hyperthyroidism. Hughes found a low rate in 77 per cent of women in the second, third, and fourth months of pregnancy and in 60 per cent up to the fifth month.

Women with a low basal metabolic rate and myxedema often have menstrual disturbances; they do not conceive. Women with a low basal metabolic rate without evidence of myxedema may suffer from severe menstrual disturbances, relative sterility, or abortion. Litzenberg and Carey noted that about a third of 137 women with a low basal metabolic rate had menstrual difficulties. These and other authors were able to avert abortion by administering thyroid extract to certain pregnant women with a low basal metabolic rate. Haines and Mussey reported a group of patients who had amenorrhea, oligomenorrhea, or menorrhagia and a low basal metabolic rate. These patients were treated only by means of desiccated thyroid in sufficient dosage to raise and maintain the basal metabolic rate at about -5 per cent. Definite improvement in the menstrual flow was obtained in 72 per cent of the cases of amenorrhea, in 55 per cent of those of oligomenorrhea, and in 73 per cent of those of menorrhagia.

Shute noted signs of mild hypothyroidism associated with an excess of estrin in the blood. He stated that the most sensitive diagnostic test for hypothyroidism is the reaction of the patient to thyroxin or thyroid extract. Patterson, Hunt and Nicodemus postulated that most thyroid disease is congenital. They concluded that: (1) the hypercholesteremia of pregnancy is due to a subclinical hypothyroidism that becomes exaggerated as the result of the increased metabolic demands of pregnancy, (2) the hypothyroid mother absorbs fetal thyroxin, producing fetal hypothyroidism from which the thyroid gland reacts to produce extreme fetal hyperplasia, and (3) the fetal thyroid hyperactivity and hyperplasia during development lead to permanent damage to the thyroid gland which, in later years and depending on the iodine supply and physiologic demands, may lead to clinically evident thyroid disease.

Carey and Brumfield, Randall, Titus, Bloss and others have successfully treated sterility among certain patients who had a low basal metabolic rate by the administration of sufficient thyroid extract to raise the rate to within normal limits. Hughes and Bloss noted an increased incidence of physical abnormalities among babies born to mothers who had hypothyroidism. The latter quoted Williams' *Obstetrics* to the effect that thyroid dysfunction results in a defective germ plasm and premature termination of pregnancy; if pregnancy continues, monstrosities result. Davis reported that low basal metabolic rates were common in the Milwaukee area and believed that a considerable number of children would have thyroid deficiency within a few years of birth if hypothyroid mothers did not receive thyroid medication during pregnancy. Bloss observed that most patients who suffered from nausea and vomiting had low basal metabolic rates and that relief was obtained upon administration of thyroid substance. This is at variance with the experience of Davis and of Falls, who noted that thyroid func-

depending on the degree of maternal hypothyroidism and the extent of failure of the iodine supply. The extent of the fetal thyroid disease will depend also on how greatly the lack of iodine may have previously affected the sperm cells or ovum or how much it affects the development and function of the fetal thyroid gland during embryonic development and throughout pregnancy. The fetal thyroid disturbance may vary from simple goiter with adequate glandular function to that total lack of thyroid development and function which is exhibited by the cretin. Mussey and Plummer have summarized the relationship of colloid goiter to pregnancy as follows: "The development of colloid or simple goiter during pregnancy may affect the future health of the mother, but it does not affect the normal progress of the pregnancy or the fetus unless the condition results in a sufficient degree of hypothyroidism to cause miscarriage or the development of colloid goiter or cretinism in the fetus."

The sources of iodine are the soil, ground water, and the sea. Sea fish have a relatively high content of iodine. The iodine content of leafy vegetables depends on the soil in which they were grown. In many regions where there is only a moderate lack of iodine, simple or colloid goiter does not become evident until the age of adolescence. Marine and Kimball and others have noted improvement or subsidence of the colloid or simple adolescent goiter following the administration of iodine. Davis and others reported that the use of small doses of iodine taken throughout pregnancy will prevent further enlargement of colloid goiter and even sometimes cause the gland to diminish in size. In regions in which colloid goiter is endemic, iodine may be supplied in the form of iodized salt which, according to Marine, should be in the proportion of one part of potassium iodide to 100,000 parts of salt. As a prophylactic for adolescents 10 mg. of iodine each week is commonly advised. Means advises one drop of compound solution of iodine (Lugol's solution) per week for adults.

Simple goiter needs no treatment except iodine during pregnancy. Frazier and Ulrich report the observations of 1,350 women who had simple goiter during early pregnancy. No complications developed as a result of the goiter and there was only one miscarriage in the group. Twelve patients underwent operation on the thyroid after delivery.

Mayo and Plummer and others have called attention to the development of new tissue, adenomatous goiter, which appears in many thyroid glands as the result of sustained stimulation in conjunction with certain unknown factors. The formation of adenomatous tissue is not common in the adolescent or more newly formed colloid goiter, but occurs with increasing frequency in women with colloid goiter as they grow older. In many of these cases, especially in the presence of large simple goiters, adenomatous nodules may be present in the gland and these may not be noticeable or may be difficult to detect. Although iodine is useful in the treatment of colloid goiter, observations indicate that the administration of preparations of iodine may cause the development of hyperthyroidism in cases of adenomatous goiter. It follows that preparations of iodine must be used with care in the treatment of adults who have large colloid goiters. For this reason Means, as previously mentioned, advised the use of one drop of compound solution of iodine per week for adults in goitrous regions.

It has been stated previously that the thyrotropic hormone of the anterior pituitary lobe governs the normal function of the thyroid gland, which is the production of its internal secretion, thyroxin. The thyroid gland, however, requires iodine for the release of this secretion. In a special article on the physiology of the thyroid in 1935, Marine quoted the work of a number of investigators on the iodine content and requirements of the thyroid gland. Oswald showed that iodine in the gland was contained in colloid and he introduced the terms "thyroglobulin" and "iodothyroglobulin." Marine and Kimball demonstrated that the iodine store "in general varied inversely with the degree of active hyperplasia; in extreme degrees of thyroid hyperplasia the iodine store was exhausted. . . . The normal human thyroid weighs from 20 to 25 gm. and the maximum storage of iodine is from 20 to 25 mg., while the average normal total store is from 10 to 15 mg." They stated that part of the iodine fed to pregnant mothers is quickly stored in the fetal thyroid.

Marine reported that work hypertrophy or hyperplasia of the thyroid gland occurs when its iodine content falls below 0.1 per cent of its dried weight. C. H. Mayo and H. S. Plummer stated, "A supply of iodine inadequate for the proper functioning of the thyroid gland, followed by a subnormal delivery of thyroxin to the tissues, produces hypothyroidism; consequent elevation of intensity of thyroid stimulation causes diffuse hypertrophy of the thyroid gland; the secretory processes are altered; the diffuse hypertrophy disappears; colloid is stored in excess of the normal, and diffuse colloid goiter is the result."

So-called simple or colloid goiter, then, is the result of the deposit of colloid substance in the thyroid gland. This occurs when a functioning gland is not furnished with sufficient iodine to enable it to discharge all the thyroxin it is stimulated to produce. In other words, the deposit of colloid substance is not an indication of lowered thyroid function but rather of a deficient supply of available iodine. The amount of ingested iodine may be barely sufficient to supply the thyroid gland under ordinary conditions and quite insufficient for the extra physiologic demand of increased metabolism which occurs at puberty, during pregnancy, and sometimes during menses and at the menopause. Under such conditions this results in the commonly noted appearance of colloid or simple goiter. When the supply of iodine is particularly meager, as in parts of Switzerland and to a lesser extent in some regions of this and other countries, there is commonly an especially noticeable enlargement of the thyroid gland during pregnancy. When the supply of iodine remains low following confinement, this deposit of colloid material does not entirely subside and even shows an increase in size during subsequent pregnancies—Tait's so-called "step-ladder" enlargement noted by Gardiner-Hill.

In cases in which colloid goiter is present, the supply of thyroxin furnished by the gland may or may not be adequate to maintain a normal average metabolism in the individual. If it is not adequate a condition of hypothyroidism exists. If the mother has colloid goiter and an adequate amount of thyroxin is produced, the fetus will not develop colloid goiter providing there is sufficient iodine for the comparatively small demand of its normally functioning gland. If the mother has colloid goiter and an inadequate amount of thyroxin is produced, the fetus will have varying degrees of thyroid disturbance

strong possibility of a thyroid crisis or subsequent infection arising outweighs the benefits of abortion; also, abortion does not cure the disease.

Starr and Patton observed remissions in hyperthyroidism induced by the injection of an extract of pregnancy urine. They suggested that the excessive secretion of estrin suppressed activity of the anterior pituitary lobe, thus in turn lessening pituitary stimulation of the thyroid gland. Bodansky and Duff, and Danforth and Loumos, working independently, noted that pregnant rats tolerated doses of thyroid extract and thyroxin which in nonpregnant controls caused rapid loss of weight and death. More than the usual incidence of stillbirths occurred in rats so treated. These experiments suggested that hyperthyroidism, at least of a mild degree, might be tolerated better in the pregnant than in the nonpregnant state.

It has been stated that hyperthyroidism resulting from adenomatous goiter is not often controlled satisfactorily by iodine and that it is safer to remove the adenomatous goiter if this condition is present. It is generally agreed, however, that exophthalmic goiter is controlled at least temporarily by the administration of iodine. Mussey, Plummer and Boothby, Means, Bothe, and Bram and others have advised the use of iodine in the treatment of exophthalmic goiter during pregnancy. In mild cases the disease may be controlled until the natural termination of pregnancy. In mild cases in which the condition is not well controlled and in severe cases following temporary improvement, subtotal thyroidectomy is indicated. Bothe, however, stated that thyroidectomy was rarely necessary during pregnancy and Bram reported that 90 per cent of patients with hyperthyroidism can be carried to normal delivery. This does not, however, agree with the findings reported by Mussey and Plummer: of 29 patients with exophthalmic goiter, only 7 (24 per cent) were carried to term on medical management. This apparent difference in the management may be only relative, as comparatively few of the latter group could be classed as having mild hyperthyroidism.

I do not find in the recent literature mention of roentgen treatment for hyperthyroidism during pregnancy. However, since roentgen therapy has been employed for hyperthyroidism in nonpregnant patients, the following statement by Means is of interest: He stated that in a follow-up investigation after roentgen treatment of 44 patients with exophthalmic goiter and of 16 patients with toxic adenomas of the thyroid gland it was found that a third were cured, a third benefited, and a third obtained no benefit. Means said that he had abandoned roentgen treatment of hyperthyroidism since the introduction of iodine in the treatment of this condition.

In the treatment of hyperthyroidism complicating pregnancy, it may be well to consider the addition of vitamin B to the medication inasmuch as Means quoted Plummer (1926) and others (including Cowgill and Palmiere, 1933, Sure and Smith, 1934) who found that at a high level of metabolism more vitamin B is required to maintain body weight.

Mussey, Plummer and Boothby have reported that the administration of compound solution of iodine in doses of 10 drops three times a day in cases of exophthalmic goiter is ordinarily followed by distinct improvement and by a definitely lowered basal metabolic rate within two weeks.

Adenomatous nodules may occur in the thyroid gland without the presence of colloid. Many persons, mostly women, may have quiescent adenomas in the thyroid gland for many years. There is a tendency sooner or later, on the average seventeen years after the tumors are first observed, for such nodules to produce an excessive amount of thyroid secretion even though the function of the remaining portion of the gland is normal. This may occur during pregnancy, or more commonly the woman may become pregnant when the adenomas are hyperfunctioning. Mussey and Plummer reported that 50 per cent of the patients with adenomatous goiter and hyperthyroidism became worse during pregnancy, whereas in only 17 per cent of cases of exophthalmic goiter were the symptoms aggravated during pregnancy. Because of the tendency for the hyperthyroidism accompanying adenomatous goiter to become aggravated during pregnancy and because the benefits of iodine in the treatment of this condition are questionable, nearly all patients with hyperfunctioning adenomas are advised to have the adenomas removed unless such patients are within the last six weeks of pregnancy. Even then if the metabolic rate is over +50 per cent, if the hyperthyroidism has been maintained for a considerable period, if there is evidence of myocardial insufficiency, or if there is dyspnea caused by pressure of the adenoma on the trachea, it is usually safer to remove the adenoma prior to delivery of the baby. An example reported by Polowe is the case of a woman with acute hyperthyroidism of the adenomatous type who was in the third trimester of pregnancy. Medical measures failed and because of the aggravated symptoms, subtotal thyroidectomy was performed. The patient was delivered safely of a normal baby twelve days after estimated term and about two months postoperatively.

Neither hyperfunctioning (toxic) adenomas nor exophthalmic goiter is a common complication of pregnancy. Wallace reported 7 true and 2 doubtful cases of thyrotoxicosis complicating pregnancy among 11,571 obstetric patients at the Brooklyn Hospital, and Frazier and Ulrich reported 35 pregnant women with toxic goiter among 4,000 who had thyroid disease at the University Hospital in Philadelphia. Pregnancy may occur during a remission in the course of exophthalmic goiter or occasionally during a mild recurrence of exophthalmic goiter following subtotal thyroidectomy.

Exophthalmic, or so-called toxic, goiter is a more frequent complication of pregnancy than is hyperfunctioning adenoma. In a series of 83 cases of hyperthyroidism complicating pregnancy observed at the Mayo Clinic there were 57 cases of exophthalmic goiter and 26 cases of hyperfunctioning adenoma. Mussey and Plummer found that hyperthyroidism resulted in relative sterility, which was estimated to be about 25 per cent of normal fertility. Also, fully 90 per cent of our patients had symptoms of hyperthyroidism prior to conception. Bram found that 66 per cent of his patients had this syndrome when pregnancy began.

It is debatable whether the degree of hyperthyroidism is decreased or increased in the presence of pregnancy. Mussey, Plummer and Boothby found that pregnancy did not render the control of exophthalmic goiter more difficult. Wallace and Bothe agreed with this when they said that abortion was practically never indicated for hyperthyroidism. In mild cases abortion need not be considered. In severe cases the

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Erratum

June 15, 1938.

Dear Dr. Kosmak:

I neglected to emphasize a point about distilled water that should have been made in the article on estrogen assay in the blood in the June issue of the THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. It is too important to pass without mention, however.

The pH of the distilled water should not be below 6.4 and the titrable acidity per liter should not exceed 20 c.c. of N/100 HCl using phenolphthalein. Ordinary laboratory distilled water usually meets such requirements. But if the acidity should be higher the difficulty may be overcome by boiling for a few minutes, allowing to cool in a stoppered container, and using while fresh.

(Signed) E. V. Shute.

London, Ontario

In the occasional case of exophthalmic goiter, within two weeks after the use of iodine a remission may follow which is complete or nearly complete, the basal metabolic rate being approximately normal or within normal limits for the period of pregnancy. In certain cases of such rapid and marked remission the patient may be carried through pregnancy by the administration of iodine. These patients must be observed carefully, however, and the basal metabolic rate must be determined occasionally as recrudescence of the disease often occurs in spite of the continued use of iodine. Except in certain cases in the last trimester of pregnancy, partial thyroidectomy should be performed without delay if the exophthalmic goiter does not show complete or nearly complete remission within two weeks after treatment with iodine is begun. A false sense of security may lead to the operation being deferred to a less favorable period of pregnancy or to a time when iodine may fail to give as complete protection against postoperative reaction, or irreparable damage to vital organs may occur. There may be exceptions to this rule in cases in which complicating conditions other than normal pregnancy exist. Whether or not operation is performed in cases of exophthalmic goiter or hyperfunctioning adenomas, aside from the judicious use of iodine the treatment is the same as that usually given to women during pregnancy and confinement.

Means has written the following concise, clear summary of the management of hyperthyroidism complicating pregnancy: "Women with toxic goiter may become pregnant, or pregnant women may become thyrotoxic. In either event it is the thyrotoxicosis, not the pregnancy, which should be interrupted. If the thyrotoxicosis is not interrupted, it often causes the interruption of the pregnancy. A pregnant woman with toxic goiter can be put through the usual routine treatment, subtotal thyroidectomy after iodination, without aborting, and proceed to go to full term normally.

"The physician is often asked whether previous toxic goiter makes pregnancy undesirable. We have seen no reason to suppose that it does. If the thyrotoxicosis has been cured there is no reason to suppose that a woman will come to any harm attributable to her past thyroid disease if she becomes pregnant. We have had a number of patients that have done so and all has gone smoothly with them. On the other hand, if there is any element at all of persistent or residual thyrotoxicosis pregnancy is undoubtedly contraindicated. It is wise to advise that a pregnancy be not undertaken until two years after the ending of the toxic goiter."

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Williams, J. T.: Epidemic Puerperal Sepsis, New England J. Med. 215: 1022, 1936.

According to Williams, puerperal infections may be divided into simple wound infections and epidemic puerperal infections usually due to *Streptococcus hemolyticus*. Operative vaginal delivery and, more especially, cesarean section greatly increase the incidence of all types of infection. Mortality is practically the same for operative and nonoperative deliveries, but much higher after cesarean section. Ordinary, or even extraordinary, aseptic precautions are not sufficient to guard against the epidemic type of infection.

No treatment, except possibly transfusion of immune blood, is of any value in epidemic *Streptococcus hemolyticus* infections. Immediate isolation of all patients showing symptoms suggestive of severe puerperal infection is the chief means of preventing development of epidemics. Culturing the throats of the staff, interns and nurses is not of much value unless the hospital has bacteriologic facilities for typing the streptococci that are found. Careful masking of all delivery room attendants is essential, although it is admitted that most of the present-day masks are inefficient.

J. P. GREENHILL.

Bonney, Victor: Puerperal Sepsis From the Viewpoint of Surgery, Brit. M. J. 1: 295, 1936.

The author contrasts the sources of infection in surgery as compared with spontaneous labor. He believes most puerperal sepsis is extrinsic and occurs after delivery. In England, for every 1,000 children born alive about two mothers die of puerperal sepsis.

The sepsis morbidity rate is 1 per cent. This is a low standard as compared to that of surgery. In a certain proportion of sporadic cases of puerperal sepsis, the infection is from an intrinsic source; "spray infection" is not the only source of puerperal infection. Extrinsic infection can readily be conquered; intrinsic sources provide more obstacles and only by adopting complete surgical methods can their menace be met. These methods consist of thorough sterilization of the approaches to the operation area, the avoidance of undue trauma, and hemorrhage in that area, and removal beforehand of septic foci of infection in other parts of the body.

The near future may provide reliable immunization prior to operation. The obstetrician should approach his cases with the same attitude that the surgeon assumes when attending an operation or taking part in it.

F. L. ADAIR AND S. A. PEARL.

Rose, J. K.: Hemolytic Streptococcic Puerperal Infection, J. Obst. & Gynaec. Brit. Emp. 44: 278, 1937.

Observations on incidence of hemolytic streptococci in lying-in women have been made by the author over a period of six years. Coordination of clinical and laboratory work insures that the presence of pathogenic organisms in patients or staff is known at the earliest possible moment and allows for more speedy and accurate diagnosis of the cause of minor symptoms and rise of temperature. In routine examination of nurses admitted for training it is found that a few in each group harbor organisms which may be a source of danger. When definite foci exist, appropriate treatment has proved effective.

In hospital patients the probable infective factors were: autoinfection in one; uncomplicated and complicated labor in four; difficult labor in two; infected attendant and complicated labor in two; and infected attendant one case. In district work the most important factor appeared to be infection in the patient or her relatives, frequently associated with anemia and general debility, the result of unsatisfactory social conditions.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Puerperium

Rivière and Legrosdidier: Azotemia and Polypeptidemia in the Puerperium, *Gynéc. et obst.* 35: 437, 1937.

This study represents a continuation of Estienny's original work and records their own subsequent researches on post-partum blood nitrogen values. In a small series of 20 normal patients, of whom 19 were delivered spontaneously and 3 by forceps under chloroform anesthesia, blood samples were taken several hours post partum, and on the sixth and twelfth days.

Puerperal elevation of blood nitrogen is physiologic and affects both urea and the polypeptids. The latter increase to a much higher level than do the former, reaching a maximum about the sixth day; both the rise and the decline of the polypeptids precede that of the urea. In the three patients submitted to chloroform anesthesia, the highest polypeptid values occurred.

The authors state that it is possible though not certain that the elevated puerperal blood nitrogen may be a humoral reflection of uterine involution. However, since the polypeptids in 50 per cent of cases become maximal within the immediate post-partum hours when the processes of involution can hardly have begun, this is not very likely. They do not believe that high puerperal polypeptid values are responsible for obstetric shock or post-partum eclampsia.

ARNOLD GOLDBERGER.

Hemmings, C. T.: A Study of Post Delivery Deaths Caused by Embolism, *Ohio State M. J.* 32: 620, 1936.

The total incidence of post delivery embolism in a series of 80,136 births studied by Hemmings was 0.04 per cent. Post delivery embolism in this study presented an incidence of 7.8 per cent of the total deaths and 14.5 per cent of the delivery deaths. The incidence of post delivery embolism was more than three times greater where operative interference was used than in normal deliveries. Cesarean section rated second in incidence of all operative procedures. Adequate prenatal care did not prevent embolism. The most outstanding causative factors in this review were hemorrhage, trauma, infection, and venous stasis. Available blood counts generally revealed a well-marked secondary anemia. Symptoms of phlebitis were present in only 24.3 per cent of the patients. Medication used had no direct bearing on the causation of embolism.

The causative factors can be prevented by: (1) A more thorough prenatal study of obesity, hypotension, anemia, and toxemia. (2) The development of better aseptic technic to prevent infection. (3) The reduction of operative interference to reduce trauma. (4) The reduction of blood loss during labor and delivery. (5) More liberal employment of blood transfusions. (6) Routine leg exercises to combat circulatory stasis.

J. P. GREENHILL.

Snoeck, J., and Rocmans, M.: Influence of the Retention of the Membranes on Puerperal Morbidity, *Rev. franç. de gynéc. et d'obst.* 32: 504, 1937.

The authors found that the total morbidity during the puerperium is the same after normal complete labors as it is following deliveries in which parts of the membranes are retained in the uterus. They believe that invasion of the uterus is useful only when there is persistence of abnormal bleeding which might indicate the possibility of retention of a portion of placenta. Exploration of the uterus for partial retention of the membranes does not ameliorate the state of the puerperium either as regards temperature or late hemorrhages.

J. P. GREENHILL.

Aisenberg-Qulianitzkaia, E. M.: The Treatment of Puerperal Septicemia by Intravenous Injections of Alcohol, *Rev. franç. de gynéc. d'obst.* 31: 777, 1936.

During the past year and a half the author observed 24 cases of puerperal septicemia, nine of which followed labor and 15 occurred after abortion. Blood transfusions were employed in 6 cases but intravenous injections of alcohol were given in all the cases. Seventeen women recovered and 7 died, giving a mortality of 37.5 per cent. The author considers this death rate a triumph for the use of alcohol and recommends this form of therapy for all cases of septicemia. He cannot explain the beneficial action of the alcohol in these cases, but it does stimulate the body activities, it supplies nourishment, it stimulates diuresis, sleep, and the appetite. The addition of glucose to the alcohol is desirable because it reinforces the action of the alcohol. The author believes that alcohol injections may also prove beneficial in cases of infectious diseases.

J. P. GREENHILL.

Livingston, Seymour H., and Blum, Samuel G.: Prophylactic Use of Ergot and Ergotamine Tartrate in Puerperium, *Am. J. Surg.* 31: 533, 1936.

On the basis of this study of 506 post-partum cases, the authors are unable to agree with other investigators who have reported marked acceleration of involution by the prophylactic use of ergotamine. However, they find that it does give a distinct reduction in the incidence of foul lochia and morbidity. Fluidextract of ergot (U. S. P.) also seems to be of some value in this respect if given intensively for a short period of time. There seems to be a somewhat more marked prophylactic effect following the use of ergotamine.

J. THORNWELL WITHERSPOON.

Voron, Pigeaud, and Burtheault: Attempt at Prophylaxis of Puerperal Infection by Means of "benzyl-amino-benzene-sulfamide," *Bull. Soc. d'obst. et de gynéc.* 26: 734, 1937.

For the past several years, in the Lyon Obstetrical Clinic, benzyl-amino-benzene-sulfamide was administered to a series of obstetric patients on the evening they were delivered, the day following, and also on the third day. In a series of 537 patients who received this prophylactic treatment the incidence of morbidity following delivery was 9 per cent. In a control group of 556 women who did not receive any prophylactic medication, the incidence of morbidity was 11.3 per cent. One patient died of puerperal infection though she had received prophylactic treatment. The authors admit that these results are not conclusive.

J. P. GREENHILL.

Leon, Juan, and Ferrari, Roberto A.: Preventive Chemotherapy of Puerperal Infection, *Bol. Soc. obst. y ginec. de Buenos Aires* 16: 300, 1937.

Sulfanilamide was administered to every patient admitted to the clinic and for four to five days post partum. In cases of ruptured membranes, immediately upon

Prophylactic measures should include: (1) Effective treatment of infections of throat and nose in those who undertake midwifery; (2) isolation in hospitals to protect the clean patients from any who are potential sources of infection; (3) prenatal treatment of the potentially infected patient if obstetric operation is anticipated; (4) early postnatal treatment of the infected patient before symptoms develop; (5) immediate investigation of contacts if swabs taken early in the puerperium show that a patient who was previously negative has acquired a new infection.

J. P. GREENHILL.

Burton, A. H. G., and Weir, J. H.: Puerperal Surgical Scarlet Fever, *Lancet* 1: 1110, 1936.

The authors give a condensed review of the subject and quote C. C. Okell on two modes of infection. The first is the ordinary scarlet fever due to a primary faucial infection, while the second is due to a primary infection of the uterus. It is recommended that the second class be regarded as a "surgical scarlet fever with the local lesion in the genital tract." From the focus of a streptococcal endometritis or a streptococcal cervicitis toxins are liberated into the general circulation and thus produce the characteristic picture of scarlatina. Locally the streptococcus produces the usual effects of a puerperal sepsis.

In the three cases reported each developed the typical syndrome of scarlet fever "including a well-marked faucial lesion, strawberry tongue, and brilliant rash followed by wide-spread desquamation." Cultures from the throat were negative for hemolytic streptococci, while those from the cervix were positive. These organisms were all inagglutinable with the ordinary scarlet fever type sera. Although all three patients were attended by the same physician, his nose and throat cultures were negative for hemolytic streptococci. Other measures to determine a possible source were not mentioned. Serotherapy gave good results and was followed by no serious complications.

In view of the authors' apparent good results with the scarlatinal antitoxin in three cases, they recommend that this therapeutic agent be further studied before condemning it as other investigators with much larger series have urged.

H. CLOSE HESSELTINE.

Wood, J. L. Miller: Puerperal Infections in Relation to Midwifery Attendants, *Brit. M. J.* 2: 811, 1937.

The bulk of serious cases of puerperal infection are due to infection with *Streptococcus pyogenes* Group A. These organisms are frequently carried by attendants and midwives. In order to demonstrate the identity of the organism swabs should be made from the cervix and throat of the patient, as well as blood cultures. Until the results are known, the midwife should cease to attend any further cases. Swabs from the noses and throats of contacts and midwife should be made. If positive for *Strep. pyogenes*, it should be typed in order to identify it and demonstrate the true source of the infection.

Midwives should be suspended from duty if they have a cold or tonsillitis or have been in attendance upon a case of scarlet fever. Bacteriologic studies if negative will permit the midwife or nurse to resume duties. The prospect of obtaining a swab-negative state from a suspended midwife or attendant is not so gloomy as might be imagined.

It appears essential in the interests of patient and attendants that all cases of pyrexia during the puerperium be investigated. The swabbing of clinically normal throats, unless they are believed to be a source of infection, cannot be too much deprecated.

F. L. ADAIR AND S. A. PEARL.

199 cases infected by hemolytic streptococci treated since these drugs were first used (1936) has been 5.5 per cent as compared with 22.8 per cent for the preceding five years.

Cyanosis developed in 58 of the 100 cases and was usually associated with met- and sulphhemoglobinemia. "Drug fever" was suspected in several instances. Prostration, paraesthesia, headache, visual disturbances, and joint pains also occurred. No generalized rashes developed.

The dosage suggested is relatively large, 8 to 15 gr. daily for the first few days in the severe infections. It should be reduced if there appears to be any adverse effect and in any case as soon as definite clinical improvement is seen.

CARL P. HUBER.

Gibberd, G. F.: Prontosil and Similar Compounds in the Treatment of Puerperal Haemolytic Streptococcus Infections, Brit. M. J. 2: 695, 1937.

The author compares the results of 1936 and 1937, when the new aniline chemotherapy was used in puerperal sepsis due to hemolytic streptococci, with those obtained in the 1934 and 1935 period. It is apparent that since the introduction of prontosil and prontylin there has been a marked improvement in the results. This is demonstrated by: (1) a fall in total mortality rate; (2) a reduction in the proportion of cases in which the infection spread beyond the limits of the birth canal, and by the relative infrequency with which an inflammatory mass developed after treatment had been instituted; (3) a significant fall in the mortality rate in cases of proved septicemia associated with a relative decrease in the proportion of severe cases of septicemia and by a fall in the incidence of septicemia developing after the treatment had been instituted; and (4) by the relative infrequency with which generalized peritonitis has been found post mortem.

These results can scarcely be explained by an assumption that the virulence of the hemolytic organism had diminished spontaneously in that period.

F. L. ADAIR AND S. A. PEARL.

Item

American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants by the American Board of Obstetrics and Gynecology, will be held in various cities of the United States and Canada on Saturday, November 5, 1938. Last day for applying is September 5.

The next general examination for all candidates (Groups A and B) will be held in St. Louis, Missouri, in June, 1939, immediately prior to the American Medical Association meeting.

Application blanks and booklets of information may be obtained from Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania. Applications for these examinations must be filed in the Secretary's Office not later than sixty days prior to the scheduled dates of examination.

this happening, and to women admitted in labor, sulfanilamide was also given. The dose used was prontosil soluble 5 c.c. of a 2.5 per cent solution; other derivatives were employed in about the same dose.

The series consists of 9 women with premature rupture of membranes, 289 women admitted during labor and 69 immediately following labor.

Intolerance to the drug was not very often seen nor was it severe. Some patients developed a slight digestive disturbance, some had slight decrease of appetite, one woman had a skin eruption. There were no changes noted in the blood or urine, but the drug was not administered to women with kidney or liver damage.

The authors feel that, in the cases studied by them, prophylactic use of sulfanilamide justified itself although further study must be made on surgical and apparently infected cases.

MARIO A. CASTALLO.

Foulis, M. A.: Prontosil Album in Puerperal Sepsis, Brit. M. J. 1: 445, 1937.

The author reports on the favorable use of prontosil tablets in puerperal sepsis. In a series of 70 such cases 22 received oral therapy. Four patients had additional prontosil soluble injections.

Of the orally treated cases 11 had septicemia; 8 had positive hemolytic streptococci in blood cultures; 3 cases of peritonitis without septicemia had hemolytic streptococci in the peritoneal fluid cultures; the remaining 7 had hemolytic streptococci in the vaginal discharge.

The dose used was high, ranging from 3 gm. (10 tablets) to 14.4 gm. every twenty-four hours at four-hour intervals. The drug was well tolerated. Toxic effects were minimal. The fall in temperature and the general improvement were rapid and striking. The mortality rate in this group was 1.4 per cent (one death) compared with 13.4 per cent in a five-year period in the same hospital.

F. L. ADAIR AND S. A. PEARL.

Drew-Smythe, H. J.: Prontosil in Obstetrics, Bristol Med.-Chir. J. 54: 217, 1937.

In spite of the possible complications that may arise from its prolonged use, prontosil and its derivatives offer a most potent agent in the prevention of morbidity and mortality associated with puerperal sepsis. The drug is not specific in its action against streptococci. Good results have been reported in cases of *Bacillus coli* pyelitis and in staphylococcal infections. Its action is obviously not that of a bactericide, but it evidently renders the infecting organisms more susceptible to attack by the natural defense forces.

The author reports a typical case of puerperal infection in which the drug was used successfully. The question of sulphhemoglobinemia is discussed. Mild degrees of psychosis have followed the use of the drug.

F. L. ADAIR AND S. A. PEARL.

Colebrook and Purdie: Treatment of 106 Cases of Puerperal Fever by Sulphanilamide, Lancet 2: 1237, 1937.

The authors report the results of treatment with sulfanilamide (para-amino-benzene sulfonamide) in puerperal infection and compare the results with those previously obtained with sulfamido-chrysoidine (red prontosil) and prontosil soluble and also with the cases treated from 1931 to 1935 when no specific treatment was used.

One hundred cases of puerperal infection due to hemolytic streptococci (92 of Lancefield Group A), 3 due to anaerobic streptococci, and 3 due to staphylococci were treated with sulfanilamide. The results are similar to those reported previously in 64 patients treated with red prontosil and prontosil soluble but a little less spectacular. Eight deaths occurred in the 100 cases. The mortality rate for the

complete individualization could we best understand her needs and therapeutic requirements. Only by adapting therapy to the individual could we feel that the patient was receiving maximum benefit from the remedial measures at our command. The idea of making the patient fit the treatment was therefore discarded and a program of individualiza-

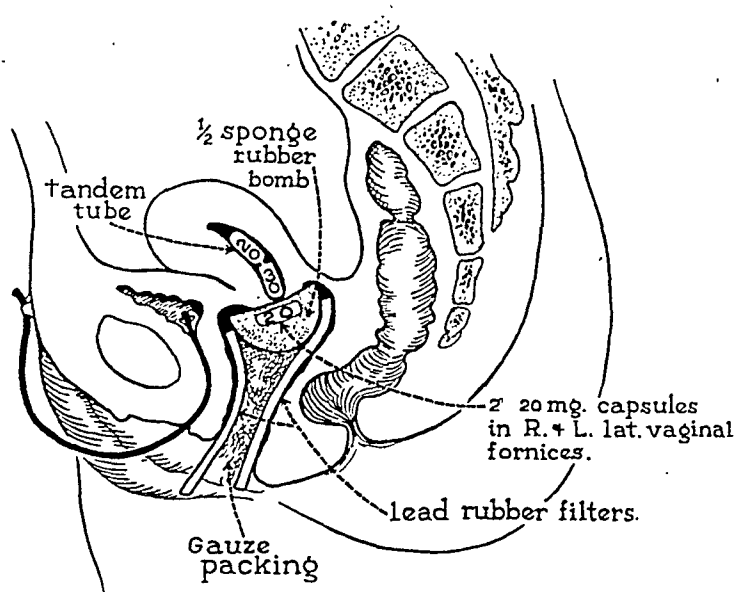


Fig. 1.—Mid-sagittal section of our radium application.

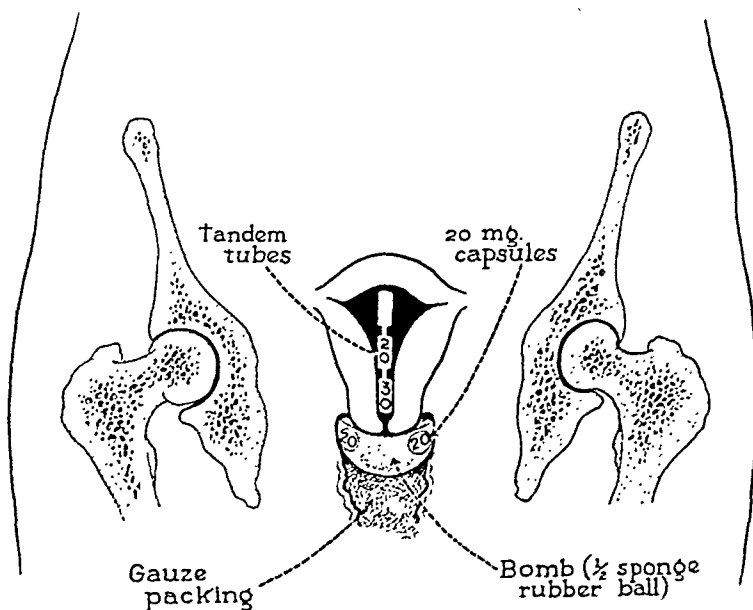


Fig. 2.—Longitudinal section.

tion inaugurated for every cancer patient admitted to the Gynecological Service at the University Hospital. It was felt that any such program, to be of real value, must include intensive study of tumor cell morphology, wide flexibility and fullest cooperation in the administration of x-ray and radium, as well as thorough evaluation of the patient's physical condition including location and extent of her tumor. To attain

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Original Communications

CARCINOMA OF THE CERVIX*

A CONSIDERATION OF CERTAIN PROBLEMS ASSOCIATED WITH ITS CONTROL

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MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan)

ANYONE familiar with the tremendous amount of data and accumulated literature regarding cancer of the cervix must be impressed with the wisdom of serious meditation before venturing to add to the complexity of the subject. Offering an intensive study of abundant material as our justification, we tender our experience with the hope that it may be of some value in the prodigious task of unravelling the truth. Our interest, first nurtured during the twilight of the surgical era and later tempered during the tidal years of enthusiasm for radiation, remains today hopeful for the future but impressed with contemporary shortcomings. For us the years 1920 to 1930 remain a period of radiation controversy. During this time we attempted to follow the leaders in this type of work. It soon became apparent that no specific form of therapy, that no one method of administration was universally suitable. At the time, being concerned primarily with results, we failed to see any good reason for limiting therapeutic measures to one mode of attack, to any one applicator or gadget, nor to any one of the then popular technics of radium or x-ray administration. It appeared to us then, and we are even more convinced of it now, that we were dealing with individuals not alone from the standpoint of the patient but also with reference to the new growth itself. Each neoplasm presented variations as to growth propensities and extent, and only by

*Read at a meeting of the Obstetrical Society of Philadelphia, February 3, 1938.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

this end our Gynecological Cancer Conference has been from the start a cooperative effort. Without the wholehearted interest and ceaseless toil on the part of our own staff and representatives from the Department of Roentgenology under the direction of Professor F. J. Hodges and from the Department of Pathology under the direction of Professor C. V. Weller, vigorous prosecution of our conference objectives could not have been so thoroughly carried out.

Since 1931 the conference group has met twice weekly at which time patients with cancer of the female generative tract have been carefully evaluated and individualized. From the time of its inauguration July 1, 1931, to Jan. 1, 1938, a total of 1,026 patients have been studied. This includes 47 patients treated prior to July 1, 1931. This mixed group makes our first conference year, i.e., 1931, of general statistical

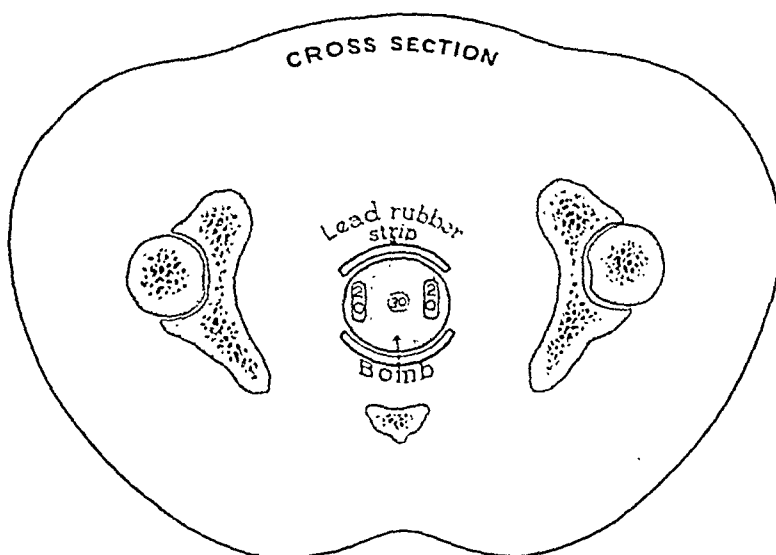


Fig. 3.—Cross section.

interest only. No attempt has been made to determine survival percentages among this group. The distribution of the lesions according to anatomic structure involved is shown in Table I. Of this total, 676 were

TABLE I. ANATOMIC DISTRIBUTION OF 1,026 CASES OF MALIGNANCY OF THE FEMALE GENERATIVE TRACT, JAN. 1, 1931, TO JAN. 1, 1938

LOCATION OF CARCINOMA	NUMBER OF CASES	PERCENTAGE
Cervix	676	64.91
Fundus	146	14.23
Ovary	94	9.16
Vagina	32	3.11
Vulva	44	4.29
Pelvis	10	1.00
Clitoris	4	0.40
Chorioepithelioma	5	0.50
Fallopian tube	1	0.10
Bartholin gland	1	0.10
Sarcoma	13	1.26
Grand Total	1,026	100.0

TABLE III. CARCINOMA OF CERVIX
ANALYSIS OF EXTERNAL RADIATION TREATMENT
JULY 1, 1931, TO JAN. 1, 1938

TREATMENT		NUMBER OF SERIES	AVERAGE NUMBER TREATMENT DAYS	NUMBER PORTS USED	INTENSITY R/MINUTE	R DOSE PER PORT PER DAY	APPROXIMATE R DOSE PER EACH PORT	TOTAL R PER SERIES
DATE	FRE- QUENCY							
Before 1931 to July 1, 1931	Daily	1-5	3-5	2	18-30 r.	100-200 r. to each of 2 ports	300 to 1000 r.	600 to 2000 r.
July 1, 1931, to July 1, 1936	2- to 4- day in- tervals	1-4	7-11	4-6	30-50 r.	150-200 r. to each of 4 ports	1200 to 2000 r.	8,000 r.
July 1, 1936, to Jan. 1, 1938	Daily	1 only	15-25	4-6	50 r.	160-200 r. to each of 2 ports	1400 to 2200 r.	7200 r. 8800 r.

We suspect that almost any of the acceptable contemporary methods of radium and x-ray therapy administration will produce about the same number of five-year survivors, that today the small statistical difference in five-year results reported by various authors is due chiefly to the extent of the lesion when remedial measures are first instituted. There does, however, exist considerable difference in the morbidity from the various methods, and from this standpoint there is abundant reason to hope for improvement.

All data regarding each patient, her lesion, treatment, morbidity and follow-up are carefully recorded on code cards and then transferred to punch cards. Complete information regarding almost any phase of the disease is thus available for any year and within a relatively short time. For five and one-half years the task of follow-up was carried by our own staff. During this time every patient seen or treated by us was traced. For the past year and one-half much of this work has been shouldered by the Hospital Social Service Department under the direction of Miss Dorothy Ketcham. We are still able to report a 100 per cent follow-up on the 676 patients with cervical cancer comprising the basis for this report. A statement regarding the tremendous difficulty of maintaining a 100 per cent follow-up is certainly apropos. Yet it would be meaningless to those who have had no experience with this problem and for those who do try to maintain a high percentage follow-up no comment is needed. Every conceivable method of locating the lost cases, from contacting bureaus of vital statistics, friends, relatives, doctors, morticians, social workers and nurses to use of detectives and radio may be found necessary. At the end of each year since the conference began (1931), a summary of the work done has been prepared. This has been thoroughly digested by the conference group with the idea of making such alterations and deductions as appeared feasible. During these seven

ening probably indicating neoplastic extension in the vast majority of cases. Twenty-seven per cent were admitted with questionable parametrial involvement, the so-called borderline group. The remaining 16 per cent was composed of Group I (4 per cent) and Group II (11 per cent) cases. Inspection of Table II will show that there occurs but little change in the clinical incidence of early and late cases from year to year. We believe this finding to be significant. It probably reflects the inefficacy of lay educational programs.

TABLE II. CARCINOMA OF THE CERVIX
CLINICAL GROUPING

CLINICAL CLASSIFICATION	YEAR OF ADMITTANCE							TOTAL
	1931	1932	1933	1934	1935	1936	1937	
Carcinoma of cervix I	7	2	4	5	2	3	5	28
Carcinoma of cervix II	11	7	10	11	10	15	12	76
Carcinoma of cervix III	29	24	23	29	32	32	16	185
Carcinoma of cervix IVA	28	46	43	50	42	44	41	294
Carcinoma of cervix IVB	8	5	11	15	10	16	17	82
Carcinoma of cervix IVC	2	2	2	0	2	1	2	11
Total carcinoma of cervix	85	86	93	110	98	111	93	676

Upon admittance to the clinic, a complete history is obtained, including the names and addresses of 5 relatives or friends. The latter have been particularly helpful in follow-up work which frequently presents tremendous obstacles. A complete physical examination, including biopsy and special studies as chest, bone, or intestinal x-rays, when indicated, complete the admittance data. The clinical aspects of the neoplasms are carefully noted and all data assembled to be presented when the patient is seen, examined, evaluated and individualized by the conference group. As previously stated this conference group, in addition to the gynecology staff, includes representatives from the departments of roentgenology and pathology. From one to ten or more patients, both new and return, may be considered by the conference during any one of its semi-weekly sessions. At these meetings a serious attempt is made to map a course of treatment best suited to the particular individual. Not only do we take into consideration the clinical grade and histologic type of the neoplasm but also the patient's age, general health, and other conditions peculiar to the individual which might bear significantly upon choice of therapy. The hospital owns 360 mg. of radium element split into a variety of satisfactory applicators and two 200,000 kv. deep therapy units. Consequently in choosing a course of therapy we are bound only by the practical limitations of this physical equipment and the patient's health. While treatment in general has followed accepted precepts, there has been no effort to treat every patient in exactly the same manner. Seventy-six per cent of our cases were treated with combined x-ray and radium. Ten per cent received x-ray only (advanced cases), 11 per cent were treated by other methods or combinations while 3 per cent received no treatment of any kind. Generally deep therapy x-ray preceded the radium application to the cervix and adjacent structures.

years of intensive study we have accumulated abundant data and no little experience. While we have no intention of bombarding a few willing readers with meaningless and tedious statistics some of our observations may prove helpful and with that thought in mind we present in this first report some general data and observations.

It will be noted throughout our tables that patients are recorded as either living or dead. We do not know how many of the living still harbor an active neoplasm but from study of survival rates we would assume a majority. In recording results some authors have the habit of speaking of survivors as "alive and free from evidence of disease." We have often wondered just where these authors include their living patients *with* evidence of disease.

An analysis of yearly admittances as of Jan. 1, 1938, is shown in Table IV. It will be noted that we see approximately 100 new cervical cancers each year. It will also be noted that we have for speculative purposes appended at the bottom of Table IV deaths due to causes other than cancer.

This was not done with any intention of presenting corrected survival rates but rather with the idea of determining just how important this correction factor really is in any completely followed large group of cases. If the percentage dead from other causes is added to the survival percentage in this table the difference is readily noted. For example our uncorrected six-year (1932) survival percentage is 24.42. When we make allowance for death from other causes we have a corrected six-year survival rate of 26.74 per cent, or almost 27 per cent. Since many of the other causes of death are directly or indirectly the result of the cancer or therapy directed toward its elimination the difficulty of deciding just which deaths are to be deducted becomes and will always remain a problem. On the other hand, where adequate follow-up is possible the quoting of "absolute" or "uncorrected" results also presents certain important drawbacks. It means the inclusion of untreated advanced cases and in some clinics this is a real item (3 per cent in our series). Furthermore, if we assume that lay educational programs may with time achieve some good so that patients will report for treatment earlier in the course of the disease the correction factor is then likely to become increasingly more important. With earlier treatment and greater prolongation of life, there will come more deaths from other causes lending greater distortion to an already controversial situation.

The 19 deaths from other causes already noted in our group were distributed as shown in Table V.

In speaking of results the casual observer thinks only in terms of survivors. This is natural and logical but it should be remembered that there are other results in the form of morbidity. Indeed, we believe this to be one of the major problems of radiation therapy today. Of the many techniques available the one that can offer the lowest morbidity will in the future become the most acceptable. With existing methods of treatment and other weapons now available the advanced cervical

apeutic methods, the very nature of cancer makes its complete destruction without costly damage to normal tissues an impractical likelihood except in early cases. To hope for a perfect cure is universal, but while we wait let's not overlook the good to be achieved through earlier treatment by existing methods.

TABLE VI. CARCINOMA OF CERVIX. MORBIDITY

JULY 1, 1931, TO JULY 1, 1937 (646 CASES)

	MORBIDITY	NUMBER OF CASES	PERCENTAGE OF CASES
Immediate	None	359	56
	Moderate	218	34
	Severe	57	9
	Treatment mortality	12	1
Late	Skin (telangiectasia)	101	16
	Gastrointestinal	440	68
	Urinary	395	61
	Bone and joint	134	21
	Peripheral circulatory	129	20
	Severe psychoses	17	3
	Severe menopausal symptoms	49	8

TABLE VII. CARCINOMA OF CERVIX. SIX- AND FIVE-YEAR SURVIVALS

CLINICAL CLASSIFICATION	SIX-YEAR GROUP 1932 TO 1938				FIVE-YEAR GROUP 1933 TO 1938			
	NUMBER CASES	NUMBER LIVING	NUMBER UNTRACED	PERCENTAGE SURVIVAL	NUMBER CASES	NUMBER LIVING	NUMBER UNTRACED	PERCENTAGE SURVIVAL
Carcinoma of cervix I	2	1	0	50.0	4	2	0	50.0
Carcinoma of cervix II	7	3	0	42.86	10	5	0	50.0
Carcinoma of cervix III	24	10	0	41.67	23	6	0	26.09
Carcinoma of cervix IVA	46	7	0	15.22	43	8	0	18.60
Carcinoma of cervix IVB	5	0	0	0.0	11	1	0	9.09
Carcinoma of cervix IVC	2	0	0	0.0	2	0	0	0.0
Total carcinoma of cervix	86	21	0	24.42	93	22	0	23.66

With prolonged and intensive study of any subject there comes a time when thoughts, rather ill-defined at first, tend to crystallize. Impressions become convictions and while often unproved these convictions may nevertheless have a real place in reshaping our ideas and furthering our knowledge regarding the subject. Our study has given us a great deal of information. It has taught us much about cervical cancer and its behavior. It has also created doubt in our minds regarding certain traditional and long accepted beliefs, a few of which, because of their general nature and bearing on the whole subject of cancer control, we venture to mention at this time.

CANCER PREVENTION FROM THE STANDPOINT OF LAY EDUCATION

To deny the value of lay education with respect to cancer is to gain-say the tremendous effort put forth by countless individuals and or-

TABLE V. CARCINOMA OF CERVIX
CAUSES OF DEATH IN 19 CASES (MORTALITY CORRECTION)
JULY 1, 1931, TO JAN. 1, 1938

CAUSE OF DEATH	NUMBER CASES
Terminal ileitis	5
Toxemia	3
Intestinal obstruction	2
Pelvic abscess (peritonitis)	2
Heart disease	2
Uremia	2
Second primary neoplasm	1
Mesenteric thrombosis	1
Pneumonia	1
Total	19

carcinoma presents an extremely poor prognosis. In the reasonably early lesion, however, there exists some choice in treatment. In both groups the morbidity is excessive and the suffering endured by many as a result of therapy, doubtfully justified. Except for the control of symptoms many advanced cases are better untreated. While on the surface it may seem cruel and heartless to deny these patients the questionable benefit of therapy, the facts show the reverse to be true. Better symptomatic treatment and alleviation of pain for these advanced cases than added suffering through ill-advised remedial measures. Potential cures among the earlier cases are common, yet many of these patients suffer unbelievable discomfort for years as a result of therapy. Naturally this cannot always be prevented, but we believe reduction of morbidity constitutes a very important challenge to therapy in the management of cervical cancer today. While we plan to consider this phase of the problem in detail at another time we should like to point out that the skeletal system as well as the skin, urinary and alimentary tracts may reflect the effects of therapeutic attack. In 1936 fourteen cases of hip fracture among patients treated in this clinic were reported. We have now seen a total of 35 proved fractures and *many* more probable fractures. Twenty-five of the proved cases occurred in the cervical cancer group. The symptomatology, pathology, and tendency to heal have been previously described elsewhere. This complication has not been generally recognized, but to us it represents but one of the many real hazards, one of the many perhaps unavoidable but nevertheless undesirable results of contemporary treatment.

Our five- and six-year survival rates are presented in Table VII. The fact that there is nothing very remarkable about our results has a very real and special significance to us. It probably closely approaches the best that we may expect to accomplish with existing remedial measures at our command and among patients of whom 84 per cent (clinical Groups III and IV) are already advanced carcinomas. These figures more than ever impress us with the need for a different approach to the problem of lay education. Even with new and vastly improved ther-

terial we have become more and more impressed with the fact that in general such cause and effect relationship is largely mythical. We have previously discussed this subject in some detail and will not repeat it here, except to call attention to certain points which bear upon the subject of cancer control. Steeped in the belief that cervical cancer starts in one of the many common lesions noted in that structure the physician is likely to overlook the fact that cancer may develop in a cervix not so afflicted. Perhaps we fail to see the trees for the woods. Cervical prophylaxis as we think of it today is desirable, but there is reason to believe that by it both patient and physician are lulled into a sense of false security. That her cervix was repaired, a scar removed or an erosion treated does not mean that the danger of cancer is over. Perhaps the glare of commonly recognized lesions blinds us to other less easily recognized abnormalities (leucoplakia) of greater significance from the precancer standpoint. To close our eyes to the shortcomings of this long accepted traditional relationship is to deny the possibility of error and clog the wheels of progress. What the dentist has done for the teeth the physician can do for the body. Nothing short of semiannual or annual pelvic examination for all women of the cancer age will pave the way for successful control of cervical cancer. Should such periodic examinations become a reality, the physician's responsibility would increase tremendously, for the early diagnosis of cancer is not easy. Consequently hand in hand with such lay response must come a much wider recognition on part of the general medical profession that biopsy is still the best available method for ruling out the presence of cancer.

CLINICAL CLASSIFICATION OF CERVICAL CANCERS

While grouping of cervical cancers has no direct bearing on its control, there exists a very important indirect relationship. Most clinical classifications today are based on *interpretation* of findings rather than findings as such and are therefore unsuitable for the vast majority of physicians. In addition groupings now in use are chiefly devoted to advanced cases which at best present a poor prognosis. We are convinced that much greater emphasis should be placed on the early lesions. In other words, a premium should be placed on those lesions offering reasonable chance for cure. The advantages of so doing are obvious. That such grouping does not yet exist is revealed in the classifications still widely used. To emphasize the need for a universally acceptable classification is not new, to proffer such a grouping is not only repetition but likely to be frowned upon. We have no desire to appear presumptuous but convinced of the desirability for a more widely acceptable basis for clinical grouping we venture to revive this rather touchy subject. Two things stand out in any consideration of this sort: (1) what we should like to do; and (2) what actually can be done as determined by the limits of practicability. Any experienced examiner of cancer patients is aware of the undesirable but nevertheless very real gap which exists between these two, particularly in those borderline cases where an

ganizations alike. The potential worthwhileness and the sincerity of purpose behind these educational efforts must be acknowledged. Yet when available data are dispassionately considered there appears to be little cause for rejoicing. The number of patients with early cervical cancers reporting for treatment continues to be low in spite of the fact that thousands of women have been made symptom conscious as a result of cancer educational movements. The fact that our own figures show practically no change of incidence in clinical groups would be of little significance, were it not that other studies reveal a similar picture. While it may be too soon to expect results from these educational drives it appears to us that there are other responsible factors. In cancer of the cervix the earliest objective evidence of trouble to the patient is irregular progressive and painless bloody spotting or other abnormal discharge. While these symptoms are generally the first noted they by no means invariably imply an early lesion. Furthermore, these symptoms are so frequently associated with other disturbances of health that their value must be considerably discounted as a means toward early diagnosis. Despite the vastly increased popular interest in cancer and the greatly improved cervical prophylaxis, the late cases still predominate. Improvement may come with time yet it seems to us that any significant change must depend on semi-annual physical examination for every woman over 35 years of age. If possible this should be achieved through education by making periodic examinations the battle cry of cancer educational programs instead of attempting to instill into a generally unscientific lay group the variable and more often unreliable symptomatology of cervical cancer. The importance of semi-annual or even yearly examination has long been recognized. It plays an important part in all health campaigns. Yet periodic examination to any real extent is probably doomed to failure at least from the standpoint of cervical cancer so long as we continue to harp on the so-called early (?) signs and symptoms.

CANCER PREVENTION FROM THE STANDPOINT OF THE PHYSICIAN

The general health benefits accruing from cervical prophylaxis cannot be doubted. The value of such prophylaxis from the standpoint of cancer prevention, however, appears to be a bird of a different feather. To question this commonly accepted cause and effect or contributing relationship will perhaps be looked upon as anything from gross misunderstanding of the subject to scientific paganism. We fully realize its delicacy and the far-reaching contingencies associated with any expression of doubt. Yet the evidence pointing to such relationship is almost entirely circumstantial. To convincingly prove this connection is obviously difficult for it has not yet been done. We do not believe the burden of proof should necessarily be borne by the supporters of this assumed relationship but would like to point out that it may be easier to disprove such affinity. Our interest in this matter goes back a considerable number of years and with intensive study of increasing ma-

2. Determination as to the existence or absence of parametrial thickening is not altogether a simple matter. In so-called borderline cases doubt regarding this point is exceedingly common. Why not recognize practical limitations in this respect and include this doubtful group as such (our Group III).

3. Interpretation of existing definite parametrial thickening is frequently impractical, often inaccurate and commonly inconsistent even among experienced gynecologists. Why not eliminate this confusion by simply reporting the non-existence, doubtful existence or definite presence of parametrial induration without attempting to interpret (guess) its significance (cancer? inflammatory?) except where the cause is obvious.

We do not deny imperfections in the classification used by us, but we believe it to be sound, universally applicable and can vouch for its practicability.

WHITHER NOW?

While we shall not attempt to answer this question there appears to be no harm in its asking. To evaluate the benefits of contemporary treatment requires only a proper viewing of the end results. This sounds simple enough and so it would be were the end results of treatment readily and truly available. While much may be learned from the abundant data already compiled, the end picture appears to be only too clearly concealed in a shroud. We do not wish to appear pessimistic. That radiation therapy produces growth restraint with prolongation of life is everywhere evident. When unassociated with excessive morbidity this extension of life span becomes one of the great benefits to mankind. In this respect radiation therapy takes its place with other great benefactions. Furthermore, in advanced cancers of the cervix, it holds a place of undisputed supremacy. Through its proper use countless doomed women are granted years of life. Among this group there is little reason for questioning its value. Here it reigns alone. It is to the minority, the small group of early, favorable cases, that our question applies. With the eight-, ten-, and fifteen-year follow-up reports of the pioneers in this field comes the growing suspicion that what is good for the late case is not necessarily good for the early case. The revelation that early cases treated by radiation when followed over a decade or more continue to show a progressive death rate from cancer cannot be viewed without concern. Among this early group there exists at least one other method of treatment, and we may well reconsider what surgery has to offer in this all too limited minority. Perhaps the swing from surgery to radium and x-ray has been too complete for the good of all concerned. In this connection the remarkable work being carried on by Dr. Frank Lynch at the University of California is worthy of serious contemplation. Unless prolonged follow-up study of early cases treated by means of radiation can show permanency of cure equaling that of surgery, it would appear that for these early cases, a return to surgery of adequate character is highly desirable.

attempt is made to determine the existence or absence of parametrial involvement. One need only record the independent findings of a group of experts on such cases to be impressed with their dissimilarity. This is because they attempt to interpret these borderline cases rather than because of any real difference in palpable findings. Interpretation varies much more than a mere statement of what is actually palpated. By basing clinical grouping on visible and palpable evidence rather than insisting upon interpretation a much more consistent and practical means of classification becomes possible. Impressed with the shortcomings of existing groupings we devised a composite classification based on what we took to be the desirable features of contemporary groupings so modified as to permit recording of visible or palpable findings without insistence upon interpretation of findings. Conceived in 1930 and used ever since we have repeatedly considered the advisability of returning to one of the older commonly accepted classifications. Each time the decision of the conference group has been to continue with our composite and modified grouping because of its practicability and consistency permitted among many examiners.

TABLE VIII. CLINICAL CLASSIFICATION OF CERVICAL CANCERS

Clinical Group I.	Any early proved lesion involving not more than one lip of the cervix or its equivalent.
Clinical Group II.	Any proved lesion more extensive than Group I, up to complete involvement of cervix but with <i>no parametrial thickening</i> .
Clinical Group III.	Group II cases with <i>questionable parametrial thickening</i> .
Clinical Group IV.	a. All cases with <i>definite</i> parametrial thickening or definite bladder, bowel, or vaginal involvement. b. Frozen pelvis, with or without remote metastasis. c. With fistula (for statistical and classifying purposes).

TABLE IX. COMPARISON WITH OTHER CLINICAL CLASSIFICATIONS

COMPOSITE (MILLER AND FOLSOME)	LEAGUE OF NATIONS	SCHMITZ	AUER
I	I	I	I
II	I	I	II
III	II	II	
IV A	III	III	III
IV B	IV	IV	IV
IV C	IV	IV	IV

Briefly, we offer the following reasons for venturing to suggest another clinical classification for cervical cancers, thus:

1. With the intense interest in cancer and the constant drive toward earlier diagnosis, by pathologists and clinicians alike, it seems advisable that we place a premium on early cases. Their desirability warrants separate classification. Yet most groupings deal chiefly with advanced cases, which form the prognostic standpoint have little to offer.

not attaching too much importance to the "five-year curability" of this disease? Should we not ask rather can this patient be returned to society a happy, comfortable woman, of use to her family, and for how long? We have at the Philadelphia General Hospital a patient who has had carcinoma of the cervix for sixteen years. During this time there have been two recurrences. Yet she has enjoyed living with her family and has served them for all of this time. Though she is undoubtedly doomed and is not a cured case, I cannot help but feel that her treatment has been brilliantly successful.

High morbidity is often the result of our zealous efforts to increase our five-year cures. At the Philadelphia General Hospital we believe that the more advanced the disease the more cautious one must be with dosage. Anspach expressed this view when he warned us to use only high voltage x-ray therapy in advanced cases.

DR. GEORGE E. PFAHLER.—An early diagnosis means more than degrees of skill or variations in the means of treatment of this disease. If we can arouse the profession at large to make frequent examinations and to pay more attention to any abnormality that is found about the cervix, a much larger percentage of early cases will be discovered.

I also am not discouraged at the lack of results from the lay education. The results have not been great because we have not yet reached the great mass of people. When we can induce all women to have a gynecologic examination twice a year or, better, four times a year, then we will surely recognize more patients in the early stage.

We are hearing a great deal today about super-voltage with 400 Kv. to 800 Kv., and we are led to expect wonderful results. I do not think we are going to change the end results very much, because such treatment is only made in advanced cases.

We know that carcinoma develops in scars in fibrous tissue, and of course, when we have treated a carcinoma of the cervix, we are leaving damaged tissue. Such damaged tissue has a lower vitality, and there is, therefore, more tendency to develop cancer in such a patient than in one who has perfectly normal tissue. After a period of 10, to 15 to 20 years, that tissue is likely to degenerate.

I agree that the palliative treatment of carcinoma of the cervix is most worth while. Some of these patients may die ultimately of carcinoma, but even so, they usually do not have the foul, sloughing carcinoma that can be diagnosed when you walk into a room. I have had the privilege of seeing patients on whom I had made a diagnosis of third stage involvement and did not estimate over 10 per cent chance of recovery, who have remained well for five or more years.

DR. CATHERINE MACFARLANE.—I wish to add further emphasis to the importance of periodic pelvic examination. With Miller, I must admit that the Campaign to Control Cancer has not accomplished the brilliant results that had been hoped for. On the other hand, I believe if Miller's statistics on this point had been carried back twenty-five years instead of five years, his conclusions would have been more valuable.

I believe certain "circumstantial evidence" has a bearing upon the significance of lacerations of the cervix in the development of cervical cancer. In a review of 1,000 white nulliparous women between 20 and 79 years of age, I found 14 cases of cancer of the cervix. In a similar series of 1,000 white parous women I found 37 cases of cancer of the cervix or almost three times as many. I should like to ask Miller how he would explain this bit of circumstantial evidence?

DR. STEPHEN E. TRACY.—Like Miller I have never believed in a standard dosage of radiation any more than I believe a patient should be made to fit some special operative technique. I was glad also to note Miller's use of the lead strips in the vagina. In our work we use 4 mm. of lead covered with 4 mm. of composition to protect the anterior and posterior vaginal walls, and we do not produce fistulas.

I differ with Miller in what he stated about the treatment of late cases. I believe that every patient should be given the benefit of irradiation, unless, of course, it is evident that the patient has but a few days to live, because once in a while a patient who seems hopeless at first visit, may be cured.

DISCUSSION

DR. BROOKE M. ANSPACH.—My belief is that the operative treatment of cervical cancer will disappear. If radium is successful occasionally in the advanced cases, why not frequently in the early ones? In our own series of Class 1 cases we had 100 per cent salvage at the end of five years.

As a result of our experience with the treatment of carcinoma of the cervix at the Jefferson Hospital, we have determined upon a plan of radiation from which we hope to get a maximum result. We use a course of deep roentgen therapy and follow it immediately with an application of radium.

Even in the early stage there may be carcinoma seedlings in the cellular or the lymphatic tissue. As the deep x-ray so obviously affects the visible carcinomatous tissue in the vagina there is certainly good reason to believe that it may favorably influence any extensions and metastases in the broad ligaments. When the pelvis is flooded with the gamma rays at the outset of the treatment the outlying seedlings of the carcinoma are at least not spread any further since there is no manipulation of the parts.

The importance of filtration now is well recognized. The ideal filter is platinum 1.5 mm. equivalent to 3 mm. of lead and with this sloughing is reduced to a minimum. The fractional principle is observed by radiating from within immediately after radiating from without. As radiation of areas that have undergone fibrosis makes trouble, the carcinomatous area should be completely radiated from without and from within before this fibrosis has had time to occur. A repetition of radiation is made only when there are projecting, easily exposed, masses of carcinomatous tissue. The dose and the screening then are such as to produce no damage to the surrounding fibrotic tissues.

As Dr. Miller has said, the results in cancer clinics all over the world are more or less the same and the longer the cases are observed the less the proportion of salvage. Ward's, Heymann's, and our own ten-year salvage do not differ appreciably.

DR. EDWARD A. SCHUMANN.—In the first place, I confess to the belief that there is no treatment for carcinoma which has any definite value. I also wonder at all of us who so gracefully grasp at the five-year study salvage. Would you salvage malignant hypertension at five years, or pulmonary tuberculosis? It is my belief that most people who have cancer of the deep tissues eventually die of cancer.

On one point only is Dr. Miller's pessimism exceeded by mine, and that is the question of periodic examination of women by physicians. "There are no early symptoms of carcinoma," says Dr. Miller, "and very often no evidence." You may paint the portio with Schiller's solution and if the cancer is a little way in the cervical canal it does not show. From time to time you make a biopsy of cancer of the cervix, but you do not get the cancer. As the otolaryngologists have sold to the people the idea of tonsils as the focus of infection and the necessity of their removal I sometimes wonder if we should sell women the idea of having amputation of the cervix the moment their families are completed?

DR. WILLIAM R. NICHOLSON.—I cannot allow one statement of the writer to pass without definite criticism. This was in regard to the value of treating lesions of the cervix. A small proportion of early carcinomas of the cervix may unknowingly be cured by the skillful use of the cautery at a stage when as far as can be seen, the lesion is nothing more than an erosion. Furthermore I am still willing to consider them as tending to the later development of cancer. It is a very grave mistake to say, at this period in our knowledge of cancer, that the presence of the lesion has no bearing upon the later incidence of carcinoma.

DR. CHARLES BEHNEY.—A great deal of time and energy has been expended in discussion of the merits of various techniques for the treatment of carcinoma of the cervix. Yet we all know that results are practically identical for cases with the same degree of involvement regardless of technique. On the other hand, comparatively little has been done to investigate palliative procedures. Are we

THE RELATION OF THE PITUITARY GLAND TO THE MENOPAUSE

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IN CONSIDERING the etiology of the menopause we are faced with three possibilities:

1. Failure of the anterior pituitary gland.
2. Failure of the end organs (uterus, cervix, vagina and the general organism).
3. Failure of the ovaries.

1. *Failure of the Anterior Pituitary Gland.*—In view of the fact that the hypophysis is the motor for ovarian function one might assume that the ovary ceases to function because of a failure of production of the gonadotropic hormones. This is not the case. The hypophysis continues its hormone production years beyond the menopause. In fact, the anterior pituitary gland secretes a greater quantity of gonadotropic hormone after the menopause than before. Large quantities of follicle-stimulating hormone can be found in the blood and urine of castrates and in those who have undergone spontaneous menopause. Hence the stimulus from the hypophysis to the ovary is present, and in adequate quantity, but the response on the part of the ovary and of the end organs to this stimulation is absent.

2. *Failure of the End Organs.*—It might be argued that the amenorrhea of spontaneous menopause is due to a failure of response on the part of the uterus, and that the amenorrhea, per se, is an etiologic factor in the production of symptoms. We may point out that menopause symptoms may be present even though the patient is menstruating at regular intervals. Amenorrhea is therefore not essential for the development of this syndrome, and patients with secondary amenorrhea do not have menopause symptoms. The genital tract of the preadolescent is capable of response providing the stimulus is great enough. In the cases of gonorrheal vaginitis in children, it has been shown that estrogenic hormones produce a temporary vaginal epithelium of mature type. The cases of precocious sexual maturity show an early response on the part of the endometrium but not the myometrium, for the uterus remains infantile (Kurzrok, 1937). On the contrary, we do not as yet know whether the atrophic uterus of a woman in the fifties (or older) would produce a progestational endometrium when adequate quantities of estrogenic and corpus luteum hormones are supplied (Hübscher, 1933). Papanicolaou and Shorr (1936) have shown that with adequate amounts of estrogenic hormones there occurs a trans-

DR. B. L. CRAWFORD.—Based on the examination of biopsies from a large number of cervical lesions, I agree with the speaker that inflammations and erosions of the cervix are not necessarily precursors of carcinoma, and that true polyps of the cervix rarely, if ever, become malignant. Because of the accessibility of the cervix every suspicious lesion of this organ should be biopsied. In studying the biopsy specimen, the change in the character of the epithelium is the most important point to consider. If the epithelium is hyperplastic and undifferentiated, the lesion should be regarded with suspicion even though actual infiltration by the epithelium cannot be demonstrated.

DR. LEWIS C. SCHEFFEY.—First, it is well enough to stress the education of the laity, but we must continue to educate the doctors. It is discouraging to the teacher to bring before students case history after case history in which patients have actually gone to a physician because of their symptoms and then, either through ignorance or indifference on his part, have not been examined or given adequate treatment or advice.

Second, whether or not one is in agreement with Miller's views regarding the significance for cancer development of certain lesions of the cervix, I think that we should definitely emphasize to our students the importance of properly treating the pathologic cervix.

DR. MILLER (closing).—We teach and stress, of course, the importance of cervical prophylaxis. Correction of minor cervical pathology is important and should be continued, but on the other hand there appears to be no good reason why we should refuse to face the facts which strongly suggest that the long accepted cause and effect relationship between common cervical lesions and cervical cancer is largely mythical. I am reminded of the words of a very distinguished anthropologist who in looking at medicine said, "I am entirely serious when I suggest that it is a very myopic medical science which works backward from the morgue, rather than forward from the cradle." If we observe common cervical lesions from early development on through involution instead of beginning with the carcinoma and working back, evidence of this assumed relationship will appear far less convincing.

I believe that time and further study will reveal little difference in the incidence of cervical cancer among women who have or have not borne children.

The vast majority of our patients receive deep x-ray therapy first. This is followed by local radiation of the lesion by means of radium. I believe radiation has much to offer the advanced case but have come to doubt that it reigns supreme as a means of treatment for the very early case. That it prolongs life and retards neoplastic growth cannot be doubted. That radiation actually cures is another question. The progressive decline in the projected survival curves of patients treated with radiation is extremely significant. On the other hand early cases adequately treated by surgical means show no such progressive decline although the initial drop may have been marked. In this connection I should like to call attention to the remarkable work carried on by Frank Lynch in San Francisco. His ten- and fifteen-year follow-up studies and the long time, follow-up studies of others are likely to change our concept as to the best method of treatment for early cervical carcinomas.

Hart (1934) have led them to believe that there are two gonadotropic hormones in the serum. The second hormone preparation used, namely, castrate urine extract (Gamone) was obtained from E. R. Squibb & Sons. It produces in animals follicles only when injected in moderate dosages for short periods.

The patients were injected with Antex-Leo either every other day or every day. Each dose contained 300 M.U. In the patients that were still menstruating injections were begun during or at the end of the period and continued to about the middle of the cycle. The essential operative procedure was performed as soon after the last injection as possible. There were neither local nor general reactions as a result of the injected material. The age, dosage and period of the cycle are given in Table I.

TABLE I. AGE, DOSAGE, AND STAGE OF CYCLE

CASE	AGE	AMOUNT OF HORMONE	DAY OF CYCLE INJECTIONS		OPERATION ON DAY OF CYCLE
			BEGAN	ENDED	
1	25	3,600 M.U.	7	18	20
2	25	3,300 M.U.	5	19	26
3	25	3,000 M.U.	3	15	18
4	26	3,300 M.U.	2	17	23
5	34	3,000 M.U.	4	15	18
6	35	1,100 (Gamone)	2	15	18
7	37	3,600 M.U.	9	22	4 of next cycle
8	43	3,600 M.U.	2	14	16
9	47	3,300 M.U.	Menopause	-----	-----
10	63	7,200 M.U.			Menopause
11	66	8,800 M.U.			Menopause

CASE REPORTS

CASE 1.—Aged 25. (No. 415102.) Gyn. Path. No. 9232, 9242, 9258, 9271.

Menses: 14 x 28 x 5 x moderate x 0. Last menstrual period, June 5 to 9, 1935.

Pregnancies: Term birth, living child, 1932.

Chief Complaint: Backache.

Diagnosis: Retroversion of uterus.

Antex-Leo: 3,600 M.U. from June 12 to 23, 1935.

Operation: June 25, 1935. Dilatation and curettage. Suspension of uterus. Right salpingo-oophorectomy.

Notes: Menses: Sept. 5 to 9, 1935; Oct. 5 to 9, 1935; Nov. 4 to 10, 1935.

Findings at Operation: The right ovary was enlarged, about 3 inches in length, and about 1½ to 2 inches in diameter. There were many new follicular cysts. The left ovary was enlarged, being about four-fifths the size of the right. In it, also, follicular cysts of new formation were found, but they were not as extensive as in the right.

Endometrium:

9232 Interval, fully developed, June 12, 1935.

9242 Interval, fully developed, June 17, 1935.

9258 Interval, possibly slightly secretory, June 20, 1935.

9271 Slight pro gravid, June 25, 1935.

Ovary: Many cysts, some large, 2 cm. In a surprising number the granulosa was present and healthy and the theca showed little or no hypertrophy.

In some, however, the theca interna had pronouncedly luteinized.

CASE 2.—(No. 474832.) Aged 25 years. Gyn. Path. No. 10111.

Menses: 11 x 28 x 3 - 4 x moderate x 0. Last menstrual periods, March 5, 1936 and April 2 to 6, 1936. No pregnancies.

Chief Complaint: Increase in size of abdomen.

Diagnosis: Fibromyomas of the uterus. Pelvic peritoneal adhesions.

Antex-Leo: 3,300 M.U. between April 7 and 21, 1936.

formation of the vaginal smear from the menopausal to that type of smear which is found in normally menstruating women during the high follicular phase of the menstrual cycle just prior to ovulation.

It is also evident that the general organism is not at fault. If sufficient follicular hormone were present, the body would utilize it. The therapeutic effect of large doses of estrogenic hormone manifests itself in a short time.

3. *Failure of the Ovaries.*—It is our belief that the menopause is due to a failure of the ovaries to react to stimuli, the gonadotropic hormones. The following questions present themselves:

a. Can the human ovary respond to gonadotropic hormones in the same manner as ovaries of other species (monkey, rat, etc.)?

b. What is the character of the response?

c. Do both ovaries in the same individual respond with equal intensity?

d. Do the ovaries of older patients respond equally as well as the ones of younger patients?

Zondek (1927) and Steinach and others (1928) have reported the experimental restoration of sexual function in old laboratory animals in which sex cycles have ceased. A reactivation of human ovaries during the menopause or shortly thereafter has been reported (Westman, 1934) but has been denied by others (Waldeyer, L., 1934).

It is important to keep in mind in considering the reaction of senile ovaries that an important difference obtains between the human and the lower laboratory animals. In all rats and mice after sex cycles have ceased, ova are still present (Waldeyer, L.) whereas, as shown some sixty-five years ago, by W. Waldeyer, ova cease to be present at or at least shortly after the menopause. To satisfy ourselves on this point, we have examined the ovaries of a number of women in and after the menopause. We have not found any ova in an extensive series of sections, although the complete serial sections of each ovary were not available. Indeed, the scarcity of ova in the latter third or fourth decade of the human reproductive period is surprising.

The reactivation of ovaries of old mice and rats might thus be expected with the administration of gonadotropic hormone. The reactivation of the senile human ovary would require the stimulation of the germinal epithelium and the new formation of ova.

MATERIAL AND METHODS

A total of 11 patients was studied. Their ages ranged from 25 to 66. They were all free from ovarian or adnexal pathology. Four patients were operated upon for the repair of retroversion and the remaining patients for uterine fibroids. The patients were injected with gonadotropic hormone, 10 with Antex-Leo, and 1 with castrate urine extract.

One gonadotropic hormone preparation which we used is derived from pregnancy mare serum, and is commercially known as Antex-Leo. This gonad-stimulating property of mare serum was first described by Cole and Hart (1930) and is the most potent gonad-stimulating substance available today. Recent results of Cole and

CASE 4.—(No. 355152.) Aged 26 years. G.P.N. 9454.

Menses: 16 x 28 x 7 - 8 x moderate x 0. Last menstrual periods, June 17, 1935; July 20 to 28, 1935; Aug. 17 to 22, 1935.

Pregnancies: One, 1933, term birth.

Chief Complaint: Lower back pain and metrorrhagia.

Antex-Leo: 3,300 M.U. between August 19 and September 3.

Operation: Sept. 9, 1935.

Diagnosis: Retroversion of uterus, postpartal.

Operation: Dilatation and curettage. Suspension of uterus. Complete right oophorectomy.

Notes: Menses October 11 to 18. Normal in all respects.

Macroscopic Examination: Right ovary measured 5 by 2 by 4 cm. Surface was smooth and glistening and yellowish in color with large and small mottled blue areas which appeared to be multiple cysts.

Endometrium: Well-developed pregravid.

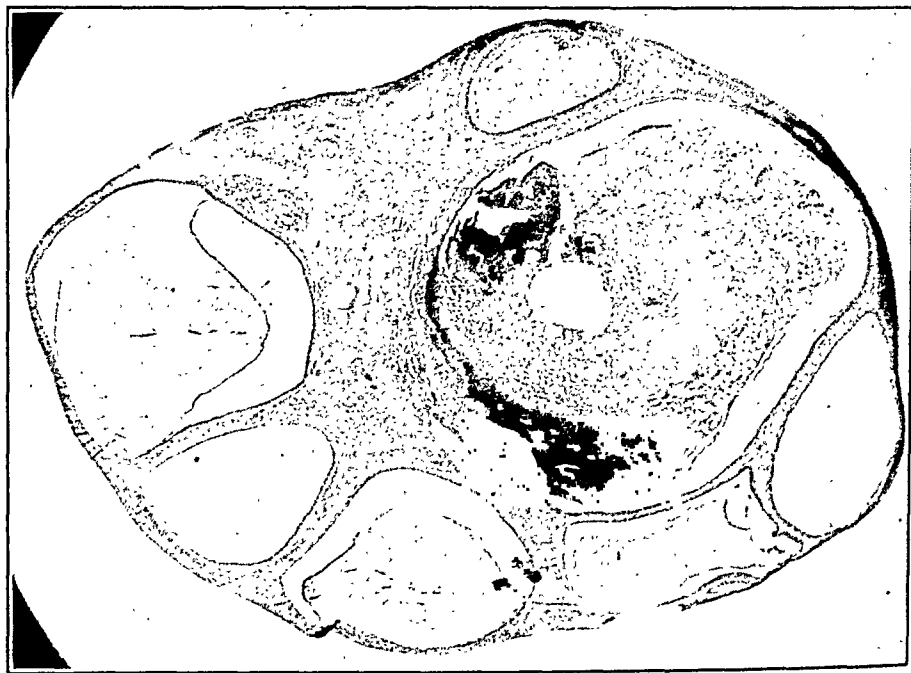


Fig. 1.—Case 3. Human ovary. G. P. N. 9546. Patient aged 25 years. Mare serum, 3,000 M. U. Large follicular cysts filled the entire ovary.

Ovaries: The other ovary was normal size. A large lutein cyst 22 by 16 mm., and there were other smaller ones which either had no granulosa or in which the granulosa was degenerating. Section B 3 (3) shows a curious follicle-like body. Some primordial follicles. Corpora albicantia present. No other lutein theca cells except in large cyst.

CASE 5.—Aged 34 years. (No. 451966.) G.P.N. 9307, 9328, 9345.

Menses: 14 x 28 x 8 x moderate x 0. Last menstrual periods, April 25, 1935; May 29, 1935; July 5 to 9, 1935.

Pregnancies: None.

Chief Complaint: Pain in back and right lower quadrant.

Antex-Leo: 3,000 M.U. between July 9 and 20.

Diagnosis: Retroversion of uterus. Salpingitis, chronic.

Operation: July 23, 1935. Dilatation and curettage. Suspension of uterus. Left salpingo-oophorectomy.

Notes: Menses, Sept. 5 to 8, 1935; Oct. 5 to 6, scant; November 5 to 8; December 9 to 10, scant; January 4 to 7; February 9 to 12; March 5 to 8.

Operation: April 28, 1936. Supravaginal hysterectomy. Bilateral salpingo-oophorectomy.

Notes: Macroscopic Examination: Right ovary weighed 26 gm. and measured 7.5 by 4.5 by 2 cm. in thickest portion. Surface was dull velvety gray in color, through which numerous petechial hemorrhages could be seen. In one area on the surface an adhesion was seen which was so fibrous it resembled calcareous deposit. Distal portion of ovary was composed of a mahogany colored cyst 2 by 2 cm., surrounded by larger areas of petechial hemorrhage. On section several follicles were ruptured; these were small and filled with clear amber-colored fluid. In about central portion of ovary two small cysts were seen filled with viscid material of dull chocolate color. Mahogany-colored cyst described contained coagulated gelatinous material, homogeneous in texture, somewhat translucent and dull mahogany red in color; edges of this cyst appeared crenated.

Left ovary weighed 20 gm. (without section taken by Dr. Cockrill). It measures 7 by 4 by 2 cm. Surface was velvety gray in color; through it numerous petechial hemorrhages were seen. Surface was entirely covered by dense adhesions. The incision previously made appeared to extend only into ovarian stroma; no cystic cavity. There were, however, small cystic cavities noted filled with clear fluid of deep amber color; largest measured about 0.5 cm. in diameter.

Microscopic: Endometrium: Early gravid.

Ovary: Corpus luteum present, apparently recently formed. Had large cavity filled with blood. Theca lutein cells distinct. Only a few places having germinal epithelium. Only a *very occasional* primordial follicle. In several of the cysts the granulosa cells were absent. In some of them the theca interna showed areas of pronounced hypertrophy but hardly formed lutein cells. No normal growing follicles.

CASE 3.—(No. 357995.) Aged 25 years. G.P.N. 9546.

Menses: 11 x 4 weeks 1 week x 4 x moderate x 0, up to 5 years ago. Last menstrual periods, Aug. 2, 1935; Sept. 4, 1935; Sept. 27, 1935.

Pregnancies: i, 1930, full term; ii, 1931, full term; iii, 1931, induced abortion; iv, 1934, induced abortion.

Chief Complaint: Backache and dysmenorrhea for past 5 years.

Antex-Leo: 3,000 M.U. between September 30 and October 12.

Operation: Oct. 15, 1935.

Diagnosis: Retroversion of uterus and relaxation of pelvic floor.

Operation: Dilatation and curettage. Repair of pelvic floor. Suspension of uterus. Right salpingo-oophorectomy. Partial left oophorectomy.

Notes: May 28, returns with history of meno-metrorrhagia.

Findings at Operation: Both ovaries were found to be enlarged to the size of bantam eggs, and there were three to four cysts on each one. A very large corpus luteum cyst was resected in the left ovary.

Macroscopic Examination: Right ovary measured 4 by 3 by 3 cm. and weighed 17.5 gm. Surface was smooth and glistening and had mottled purplish white color. Ovary was very fluctuant; it appeared on the surface as though many cysts were present 0.5 to 2 cm. in diameter. On one side of ovary was a rather solid hemorrhagic appearing area. On section a number of cysts were seen filled with clear fluid.

Corpus luteum taken from left ovary measured 2.5 by 1.5 by 1 cm. and weighed 2 gm. It had a shiny glistening purplish external surface. Wall was 7 cm. thick; lumen about 0.5 cm. in diameter.

Microscopic: Ovary: A large corpus luteum filled with blood which contained an empty cyst lined by simple squamous epithelium. A large corpus luteum hemorrhagic and with much fibrin. There were many cysts in which granulosa was decreased or was absent. In the largest cyst the theca interna (?) at one side had undergone luteinization. In some others the theca interna cells were somewhat or greatly hypertrophied as if they would luteinize. Some very small (5 mm.) cysts had no granulosa. A small number of primordial follicles but no normal growing ones. Cysts, largest 15 mm. Most under 1 cm. (5-8 or 10 mm.).

Endometrium: A typical highly developed proliferative type.

Operation: April 17, 1936. Dilatation and curettage. Supravaginal hysterectomy. Left salpingo-oophorectomy.

Findings at Operation: Patient menstruating. Right ovary small and pale without significant follicles. Left ovary was normal in size and had two small cysts.

Macroscopic Examination: Ovary measured 3 by 3 by 1.5 cm. External surface was smooth and glistening; it was covered by number filmy adhesions. It felt somewhat cystic and contained a cyst 2 cm. in diameter filled with bloody fluid. Internal surface was smooth and glistening and was purplish red in color.

Endometrium: Pro gravid probably menstruating.

Ovary: A degenerating recent corpus luteum was present. A cyst (ruptured) was present. The poorly developed lutein-like cells were probably from the theca interna. No normal primordial follicles were found in the 4 sections of the ovary available. A very occasional degeneration was present. No normal growing follicles. Cysts had little or no granulosa and theca interna showed hypertrophy in some.



Fig. 2.—Case 8. Human ovary. G. P. N. 9298. Patient aged 43 years. Mare serum 3,600 M. U. Only one very young corpus luteum and numerous corpora albicantia.

CASE 8.—Aged 43 years. (No. 300265.) G.P.N. 9281 and 9298.

Menses: 16 x 28 x 3 x moderate x 0. Last menstrual period, June 19, 1935.

Chief Complaint: Pain in left lower quadrant.

Antex-Leo: 3,600 M.U. had been given between June 20 and July 3, 1935.

Diagnosis: Retroversion.

Operation: July 5, 1935. Supravaginal hysterectomy. Bilateral salpingo-oophorectomy. Dilatation and curettage.

Pregnancies: i, 1912, miscarriage; ii, 1913, term birth; iii, 1916, term birth; iv, 1917, miscarriage.

Progress Note: Menopause symptoms developed soon after operation and patient was seen regularly in the clinic for the relief of these symptoms.

Findings at Operation: There were numerous fine adhesions over the top of the fundus, as well as on its posterior surface. In several places, the omentum was attached to the fundus. Small areas of encysted peritoneal fluid were noted along the posterior wall of the uterus. Both tubes and ovaries were bound down to the lateral walls of the pelvis with fine adhesions. In other respects, the tubes were normal appearing. The left ovary contained a 1 cm. hemorrhagic cystic area

Findings at Operation: The ovaries were not increased in size, but both appeared to be filled with small cysts.

Upon inspection of the pelvis, the uterus, tubes, and ovaries were found to be densely adherent to the posterior peritoneum.

Macroscopic Examination: Ovary measured 4 by 2 by 2 cm. Surface was smooth and glistening. It was made up of a number of small bluish cysts.

Endometrium: 9307, Typical pro gravid. 9328, Very hemorrhagic. Apparently only superficial tissue. Except for the large number of polymorphs in the stroma and in the gland lumina, it appeared to be typical proliferative endometrium.

Ovary: A hemorrhagic and degenerating corpus luteum from the previous cycle is present.

There were some but not many primordial follicles. A very occasional small follicle with antra, 2 seen in sections. The most noteworthy feature was the number of cysts present. All of these had a thin granulosa (2 to 4 cells thick). They varied from 3 to 7 mm. in diameter. No or but little thecal hypertrophy and no luteinization of the granulosa or theca interna.

CASE 6.—Aged 35 years. (No. 464109.) G.P.N. 9679.

Menses: 14 x 27 x 4 x moderate x 0. Last menstrual periods, Oct. 17, 1935, and Nov. 11 to 14, 1935.

Pregnancies: Questionable early abortion five years ago.

Chief Complaint: Mass in right lower quadrant. Pain in both lower quadrants. Vaginal discharge.

Operation: Nov. 29, 1935.

Castrate Urine Extract: Squibb, 1,100 R.U. given between November 12 and 26.

Diagnosis: Fibromyomas of uterus.

Operation: Dilatation and curettage. Supravaginal hysterectomy. Right salpingo-oophorectomy.

Notes: No menopause symptoms six months after the operation.

Findings at Operation: The left ovary was normal in size, and upon its anterior surface were seen five cysts, bluish-black in appearance, averaging 1½ cm. in diameter. The right ovary was enlarged to about the size of a lemon and its surface was studded with cysts resembling the others, but much larger in size. It was decided to remove this ovary.

Macroscopic Examination: Ovary measured approximately 3.5 by 2.5 by 2 cm. Surface was smooth and glistening. Part of surface was yellowish gray in color; proximal and lower two-thirds, however, have been converted into cystic mass. On external surface they appeared as small globules which were seen beneath the tissue as bluish gray in color. At outer pole was a small corpus luteum deposit showing hemorrhage on external surface. Ovary was cut with slightly less than normal resistance; cut surface was reddish gray in color and very moist and appeared quite cystic. Several small cysts were opened; they measured 1 cm. in diameter and contained bloody serous fluid. Inner surface was lined by smooth glistening purplish gray membrane; several small whitish areas were seen, one having been cut through. Here the top tissue was grayish white in color and stood up somewhat from the cut surface.

Left ovary was normal in size.

Endometrium: Interval, early pro gravid?

Ovary: Several cysts. In some the granulosa had disappeared and in others, it was present and had a normal appearance or showed degeneration. The theca interna cells were very slightly, if any, hypertrophied.

CASE 7.—Aged 37 years. (No. 476697.) G.P.N. 10071.

Menses: 14 x 28 x 4 x moderate x 0. Last menstrual periods, Dec. 20, 1935; Jan. 17, 1936; Feb. 14, 1936; March 2, 1936; March 22, 1936; April 13, 1936.

Pregnancies: Stillbirth, twins, fifteen years ago.

Chief Complaint: Pain in left lower quadrant.

Antex-Leo: 3,600 M.U. between April 1 and 13.

Diagnosis: Fibromyomas of uterus.

no growing follicles but several small cysts. The four remaining cases (patients 43, 47, 63, and 67 years old, respectively) showed no response on the part of the ovary whatsoever, even though the oldest patient received 8,800 M.U. of Antex-Leo. The reactions were greatest in the third decade of life, a slight response was present in the fourth, and a total absence of response in the fifth decade and beyond. A response may be maximal on one side and absent on the other.

4. Microscopic examination of the follicle cysts showed: (a) An absence of ova (in the sections examined to date). (b) Degenerative changes in the granulosa of varying degree. Most often there was a loss of the granulosa layer, with only one layer of cells remaining. Occasionally there appeared patchy areas of normal appearing granulosa. (c) There occurred luteinization of the theca interna and occasionally of the granulosa. Such luteinization may be associated with a pregravid endometrium. (d) One patient, Case 2, 25 years of age, showed early luteinization of the theca interna plus the granulosa layer.

5. One patient, Case 6, 35 years of age, injected with 1,100 units of castrate urine extract (Squibb) showed a cystic enlargement of one ovary to the size of a lemon, and a grossly normal ovary on the opposite side. The theca interna cells show no definite change.

CONCLUSIONS

1. The human ovary showed a loss of response to gonadotropic stimulation with age. There is a slight response in the fourth decade, and a complete absence of response in the fifth decade and beyond.

2. When the response is definite, only one ovary may show this response, while the other may show no stimulation at all. This implies the concept that one ovary can cease function before the other.

3. The injections did not induce the formation of normal follicles but resulted in multiple cysts (in the reactive ovaries) varying from 5 mm. to 2 cm. in size.

4. The menopause is due to a loss of response on the part of the ovary to gonadotropic hormones.

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at one pole. Along its surface, there were several small brownish areas, grossly suggestive of endometriosis. The right ovary was normal appearing.

Macroscopic Examination: Right ovary measured 3 by 2 by 1.5 cm. It was covered by very dense adhesions, and was dark red in color with purplish discoloration. On section there appeared to be a hemorrhagic cyst 1 cm. in diameter and a smaller cyst 0.5 cm. in diameter.

Left ovary measured 3 by 1.5 by 2.5 cm. It was pale.

Endometrium: 9281, Interval (?) phase. Stroma very loose. Surface epithelium low. 9298, Interval type. Stroma dense, nuclei large. Surface epithelium high.

Ovaries: Several corpora albicantia. No growing follicles or primordial follicles. No cysts. A number of corpora albicantia. A small apparently recently formed corpus luteum which was hemorrhagic. No cysts. No growing or primordial follicles. Germinal epithelium very flat.

CASE 9.—Forty-seven years of age. Dementia precox. Irregular menstruation during past year. Jan. 20 to 30, 1936, 11 injections Antex 300 M.U. per day (total 3,300 M.U.). February 3, supravaginal hysterectomy. Bilateral salpingo-oophorectomy.

Surgeon's Report: Uterus 3 times normal size. Multiple fibroids. Right ovary, average size, no follicles observable. Left ovary, somewhat enlarged. Two cysts 1 cm. in diameter, 1 clear and 1 hemorrhagic.

Anatomy: Right ovary (Bouin). 4.03 gm. 25 by 18 by 15 mm. Some small cysts. Left ovary 6.37 gm. 30 by 25 by 15 mm. Two cysts. Each had a single layer of granulosa cells. No thecal hypertrophy. Both ovaries had corpora albicantia of varying sizes.

CASE 10.—Sixty-three years of age, colored, widow. Manic depressive psychosis. June 10 to 21, 1935, Antex 600 M.U. per day for twelve days (7,200 M.U. total).

Operation: June 24. Uterus and ovaries out.

Surgeon's Report: Ovaries totally inactive. In right ovary was a retention serous cyst.

Anatomy: Right ovary, 2.82 gm., 30 by 22 by 10 mm. Left ovary, 1.35 gm., 19 by 14 by 10 mm.

Several corpora albicantia in each ovary. No follicles or cysts except in right ovary. No granulosa or theca interna distinguishable.

CASE 11.—Sixty-six years of age. Colored. Dementia precox. April 5 to April 17, 1935, 8,800 M.U. of Antex.

Operation: Following day. Uterus and ovaries out. Uterus with fibroids. Ovaries small and unchanged by the injections.

Anatomy: Right ovary, 3.19 gm., 25 by 22 by 11 mm. Left ovary, 2.50 gm., 20 by 19 by 13 mm. No follicle or cysts visible. Several corpora albicantia present.

RESULTS

The following results were obtained:

1. There were no normal follicles.

2. The ovaries *when they reacted* showed follicle cysts. These varied in size up to 2 cm. in diameter. There were several in each ovary. The ovaries of our youngest patients were 7 to 8 cm. in diameter (immediately after removal).

3. In the three youngest patients (each 25 years of age) both ovaries showed grossly a similar reaction. In a fourth patient (26 years old) only one ovary showed a marked cystic enlargement and the other ovary appeared normal. Two other cases (patients 34 and 37 years old, respectively) showed a slight enlargement of both ovaries. They have

are compensatory mechanisms, the first designed to bring more oxygen to the blood and the second to deliver more oxygen to the tissues. With increasing anoxemia a point is reached when these compensatory mechanisms fail to supply oxygen in amounts sufficient for cellular oxidation and then, with dramatic suddenness, "the oxygen crisis" of the physiologists, or what is termed the "reversal" by Schmidt, takes place and after this events occur rapidly. Consciousness is lost and respirations stop. Following respiratory failure there is an interval of from three to five minutes during which the heart continues to beat, but there is a marked slowing of the rate. In a typical case the slowing occurs by abrupt steps from 156 per minute before the crisis to 44 per minute in the posterisis phase. After respirations cease, sometimes a little earlier, the blood pressure rapidly declines through forty to sixty seconds. Concomitant with the drop in blood pressure the skin becomes blanched and cold, as in shock. Early in the posterisis phase of experimental anoxemia another important change occurs: the nerve muscle endings of skeletal muscle cease to function, with complete collapse of that muscular system. This results, of course, not only in flaccid extremities, but in relaxation of the sphincter ani. To recapitulate, experimental anoxemia presents the clinical picture of asphyxia neonatorum in its entirety, namely: unconsciousness, apnea, bradycardia, limp extremities, relaxed sphincter ani and the white, cold skin of shock.

The close similarity, if not identity, between asphyxia neonatorum and experimental anoxemia made it seem worth while to study the comparative value of pure oxygen and of various carbon dioxide mixtures in the resuscitation of dogs which had been rendered apneic by anoxemia. The points of particular interest for investigation were:

1. The time required to establish spontaneous breathing when various gas mixtures were used in artificial respiration.
2. The character and permanence of the re-established respiration. It has been claimed that the employment of pure oxygen in resuscitation may cause a "washing out" of carbon dioxide with resultant "acapnea." It seemed important to determine whether the re-established respirations reflected evidence of this or other abnormalities.
3. The effect of breathing 25 per cent carbon dioxide for short periods.

DESCRIPTION OF METHODS

Dogs weighing between ten and twelve pounds were anesthetized lightly with chloroform and strapped to the operating table in the usual supine position. The trachea was exposed, opened and a cannula inserted, through which nitrous oxide, oxygen, and if necessary ether were administered. Fluctuations in blood pressure were recorded in the usual manner by means of a cannula in the right femoral artery connected with a mercury manometer and slowly revolving kymograph.

Around the animal's chest and upper abdomen was placed a rubber bag which was secured in place by a loosely tied cloth casing. The bladder was inflated slightly and connected to a large tambour by means of a rubber tube, the conducting medium being air. To the rubber membrane of the tambour was affixed a pointer which recorded the respiratory excursions.

THE RELATIVE VALUE OF PURE OXYGEN AND OF CARBON DIOXIDE MIXTURES IN EXPERIMENTAL RESUSCITATION*

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THE relative value of pure oxygen and of various carbon dioxide mixtures in the treatment of asphyxia neonatorum has been a subject of controversy for some years. On the one hand, Yandell Henderson¹ strongly advocates the use of carbon dioxide mixtures, recommending concentrations of this gas in oxygen which range from 7 to 20 per cent. He contends that carbon dioxide is the physiologic respiratory stimulant and believes that its stimulating effect is particularly needed in asphyxia neonatorum, because the sensitivity of the respiratory center is depressed in that condition.

Recently McGrath and Kuder² have reported observations on apneic newborn infants which were resuscitated by means of carbon dioxide mixtures, and their results lead them to concur in Henderson's views. On the other hand, Eastman,³ Kane and Kreiselman,⁴ and others, have advanced evidence which seems to indicate that pure oxygen, rather than carbon dioxide mixtures, is the ideal gas for resuscitation in asphyxia neonatorum. They base their contentions on the following considerations:

1. Actual chemical studies on the blood of truly asphyxiated infants reveal that it is already overloaded with this gas; whereas normal newborn infants have blood carbon dioxide tensions varying from 38 to 60 mm. of mercury, the blood of asphyxiated infants shows carbon dioxide tensions in excess of 65 mm., concentrations so high as to be scarcely compatible with life; to augment this excess of carbon dioxide by administering still more of the gas would seem illogical and possibly unsafe.

2. In the presence of anoxemia, which is found to a marked degree in asphyxia neonatorum, the usual respiratory stimulants, such as carbon dioxide, are known to become respiratory depressants (the "reversal" of Schmidt⁵).

3. Clinical evidence in the main indicates that pure oxygen is superior to carbon dioxide mixtures in the resuscitation of newborn infants.

In the severer forms of asphyxia neonatorum the blood is almost depleted of oxygen. Perhaps the most striking evidence of the major role played by anoxemia in asphyxia neonatorum lies in the fact that the whole clinical picture of the condition may be reduplicated both in the human being and in lower animals by reducing the blood oxygen.⁶ The sequence of events in experimental anoxemia may be described as follows: To mild degrees of anoxemia the body reacts by increased respiration and accelerated heart rate; these presumably

*Read by invitation before the Washington Gynecological Society, Nov. 27, 1937.

asphyxiation and resuscitation well, and it was usually possible to repeat the procedure six or more times. On the other hand, when carbon dioxide mixtures were employed in resuscitation, it was frequently observed that the re-established respiration was of an irregular and convulsive type. Not uncommonly it became more and more shallow, terminating in a recurrence of the apnea. This gasping, irregular type of breathing, which frequently follows experimental resuscitation with carbon

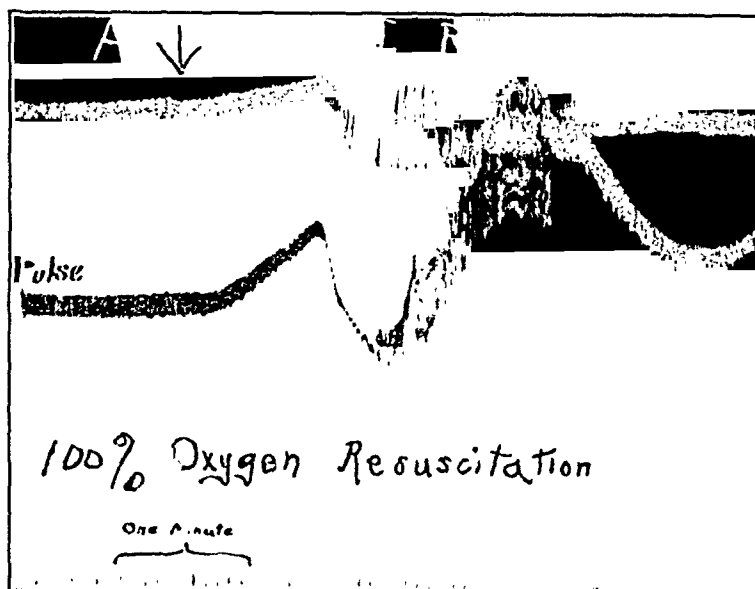


Fig. 1.—Showing the oxygen crisis of experimental anoxemia followed by resuscitation with 100 per cent oxygen. Asphyxiation is started at A. Within two minutes the blood pressure, together with the pulse pressure, falls (lower tracing), while respiration ceases (upper tracing). At I artificial respiration is begun, spontaneous breathing being initiated at R. The restored respiration is normal in rate and rhythm and remains permanently established. The blood and pulse pressures also return to normal.

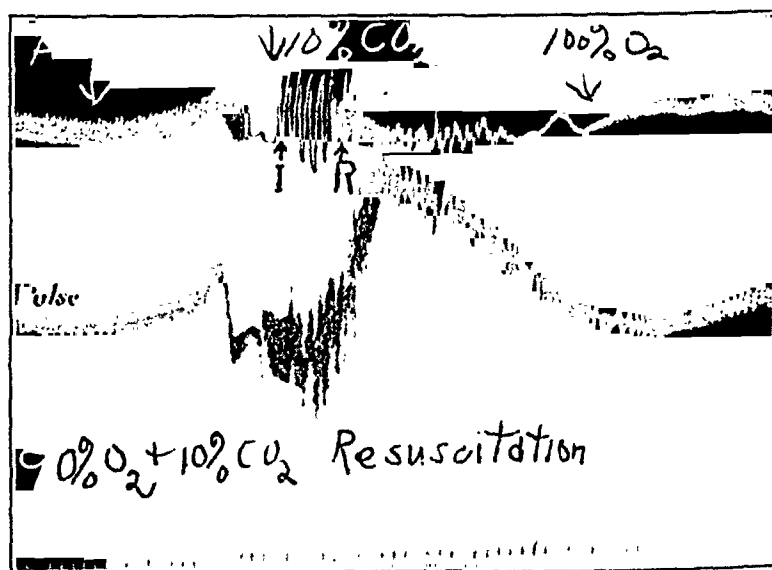


Fig. 2.—Showing the oxygen crisis of experimental anoxemia followed by resuscitation with 10 per cent carbon dioxide in oxygen. Asphyxiation is started at A. Within two minutes the blood pressure, together with the pulse pressure, falls (lower tracing), while respiration ceases (upper tracing). At I artificial respiration is begun, spontaneous breathing being initiated at R. The restored respiration is irregular and convulsive in type and soon becomes shallow, while the pulse pressure shows irregularities. Improvement follows the administration of 100 per cent oxygen.

Asphyxiation was accomplished by allowing the dog to breathe 100 per cent nitrous oxide. For our purposes nitrous oxide seemed preferable to nitrogen as an asphyxiating agent for the following reasons: (1) Its anesthetic properties obviated the necessity of using other anesthetics during asphyxiation. (2) Clinical asphyxia neonatorum occurs most often in cases in which the mother has received analgesics and anesthetics; among these, concentrated mixtures of nitrous oxide not infrequently produce this condition; accordingly, the employment of this gas for asphyxiation would seem more nearly to reproduce the circumstances of asphyxia in the newborn. (3) Preliminary experiments showed that oxygen crises produced by nitrous oxide resembled closely those brought about by nitrogen, with the exception that nitrous oxide asphyxiation caused an earlier breakdown of respiration. It would seem then to offer a more severe test to any method of resuscitation used.

Following the administration of 100 per cent nitrous oxide, oxygen crises, with marked fall in blood pressure and apnea, occurred in all experiments within two to three minutes. After breathing had ceased for approximately thirty seconds, artificial respiration was instituted with a Kreiselman resuscitator,⁷ various gas mixtures being employed. In a small series of experiments, artificial respiration was withheld until sixty seconds of apnea had transpired.

At the depth of the oxygen crisis, blood samples were taken from the left femoral artery for oxygen determination. These showed oxygen which ranged between 2.3 and 4.0 volumes per cent; in severe asphyxia neonatorum the oxygen levels of the umbilical vein blood varies between 0.5 and 4.0 volumes per cent.³

RESULTS

1. *The time required to establish spontaneous breathing when various gas mixtures were used in artificial respiration:* Pure oxygen was administered in 92 experiments on 27 animals; the average time required to re-establish spontaneous breathing was forty-six seconds. Ten per cent carbon dioxide in oxygen was administered in 38 experiments on 20 animals; the average time required to re-establish breathing was fifty-two seconds. Twenty-five per cent carbon dioxide in oxygen was employed in 23 experiments on 15 animals and the average time necessary for resuscitation was forty-nine seconds. Thus, from the standpoint of time, the results obtained with pure oxygen and with carbon dioxide mixtures were almost identical when the period of apnea was thirty seconds. The results of two typical experiments, in one of which pure oxygen was used as the resuscitating gas and in the other 10 per cent carbon dioxide, are shown in Figs. 1 and 2.

As noted above, a small series of 8 animals were subjected to asphyxial apnea for sixty seconds. In four of these animals resuscitation was first attempted with 10 per cent carbon dioxide. When this gas alone was used, success was met in but one experiment out of the four and this after two minutes. In two instances, after three minutes' insufflation with 10 per cent carbon dioxide had failed to initiate spontaneous breathing, pure oxygen was administered and respiration began within ninety seconds. In the fourth experiment, cardiac action ceased after two minutes of attempted resuscitation with 10 per cent carbon dioxide. In the remaining four animals, resuscitation was attempted with 100 per cent oxygen. Spontaneous respiration was established in 3 cases after one minute, ninety-five seconds, and two minutes, respectively. In the fourth animal the administration of pure oxygen for three minutes was unsuccessful; this was followed by insufflation with 10 per cent carbon dioxide, but the animal died two minutes later. Individual variations in the ability of animals to withstand asphyxiation make conclusions in this group difficult. The observations suggest, however, that pure oxygen is preferable to 10 per cent carbon dioxide as a resuscitating agent when the asphyxiation is profound.

2. *The character and permanence of the re-established respiration:* When pure oxygen was used as the resuscitating gas, the re-established respiration was regular and apparently normal in character, as may be seen in Fig. 1. It was sustained indefinitely and in no instance was further resort to artificial respiration necessary. The blood and pulse pressures returned quickly to their normal levels. These animals which had been resuscitated with pure oxygen withstood subsequent

lowing resuscitation by carbon dioxide, the pulse pressures failed to return to their previous configuration and showed decided irregularities for five minutes or more. These animals, moreover, withstood subsequent asphyxiation and resuscitation poorly, and it was rarely possible to repeat the procedure more than three times without losing the animal. Our observations, therefore, afford no foundation for the contention that resuscitation by pure oxygen causes a "washing out" of carbon dioxide with resultant apnea. In our ninety-two experiments with pure oxygen nothing suggestive of such a phenomenon was observed. On the contrary, as we have indicated, it was only when carbon dioxide mixtures were used for resuscitation that abnormal types of respiration ensued.

3. *The effect of breathing 25 per cent carbon dioxide for short periods:* Since mixtures of 25 per cent carbon dioxide, or even more, have been recommended for the treatment of asphyxia neonatorum^{1,13} and since it is occasionally necessary to employ artificial respiration in these cases for long periods, it seemed desirable to observe the effect of this gas when administered to animals in high concentration over certain intervals of time. Six animals were allowed to breathe a gas mixture containing 25 per cent carbon dioxide and 75 per cent oxygen for periods varying between seven and fifteen minutes. As is shown in Fig. 4 marked stimulation of respiration immediately followed. Soon, however, gasping respiration occurred and the animal became cyanotic, while the blood pressure fell. In the experiment illustrated the carbon dioxide mixture was withdrawn after seven minutes and air substituted; nevertheless, the respiration became more and more shallow and death followed shortly. Two other animals died after breathing 25 per cent carbon dioxide in oxygen for fifteen minutes. Similar experiments were carried out more than fifty years ago by Friedländer and Herter⁸ with comparable results.

DISCUSSION

It is well known that carbon dioxide produces toxic effects even when breathed in weak concentrations. Continuous breathing of an atmosphere containing 1 per cent carbon dioxide will incapacitate men for work and 6 per cent will usually cause subjective symptoms of malaise, headache, nausea, and even unconsciousness. Brown⁹ has found that the majority of men working in submarines were completely incapacitated when 6 per cent concentrations of carbon dioxide were reached. Noticeable hyperpnea occurs when the inspired air contains as little as 2 per cent and as the concentration reaches 10 to 15 per cent distinct dyspnea results; but beyond this point further concentration of carbon dioxide, instead of augmenting respiration, decreases it. When concentrations of 40 to 50 per cent are reached death occurs at once, without convulsions, but with the appearance rather of a fatal narcosis. In Howell's¹⁰ opinion it is probable that carbon dioxide in these concentrations exercises a direct toxic action on the nerve cells. Recently Becker¹¹ has shown that the toxic effect of carbon dioxide is not dependent upon its acid character but upon other properties: a specific lethal action on protoplasm coupled with an ability to penetrate cell boundaries with extreme rapidity. In the presence of anoxemia the harmful effects of carbon dioxide become accentuated. Schmidt⁵ has shown that when the oxygen content of the blood has been lowered sufficiently to bring about an oxygen crisis, carbon dioxide becomes a respiratory depressant. Recent experimental studies by Gellhorn¹² indicate that under conditions of oxygen deficiency 3 per cent carbon dioxide in the inhaled air increased the fall in body temperature over that observed in oxygen

dioxide mixtures, is shown in Figs. 2 and 3. In our experience it persisted for one or two minutes after the onset of spontaneous breathing (R) and then changed into a regular but shallow type of breathing. In both of these experiments it became so very shallow that administration of 100 per cent oxygen was deemed necessary to save the animal; apparent improvement in the respirations then occurred. Fol-

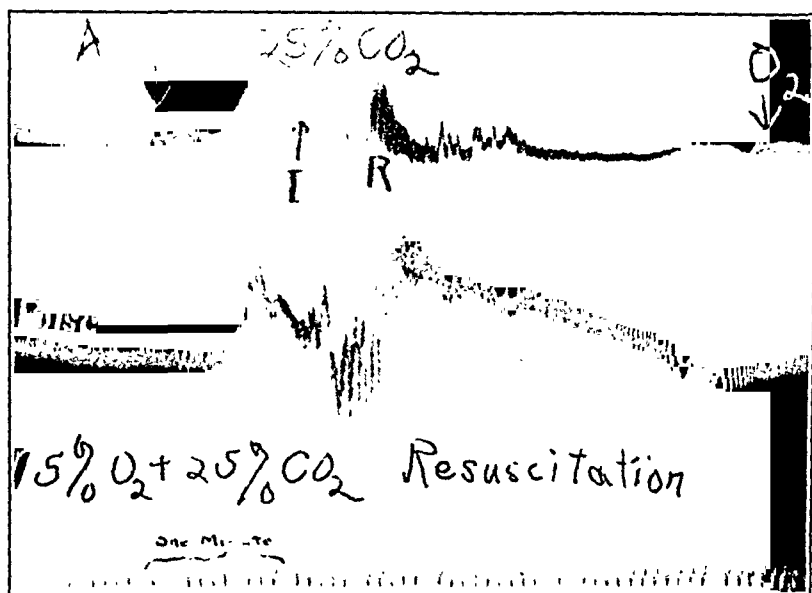


Fig. 3.—Showing the oxygen crisis of experimental anoxemia followed by resuscitation with 25 per cent carbon dioxide in oxygen. Results similar to those shown in Fig. 2. Symbols the same as in Figs. 1 and 2.

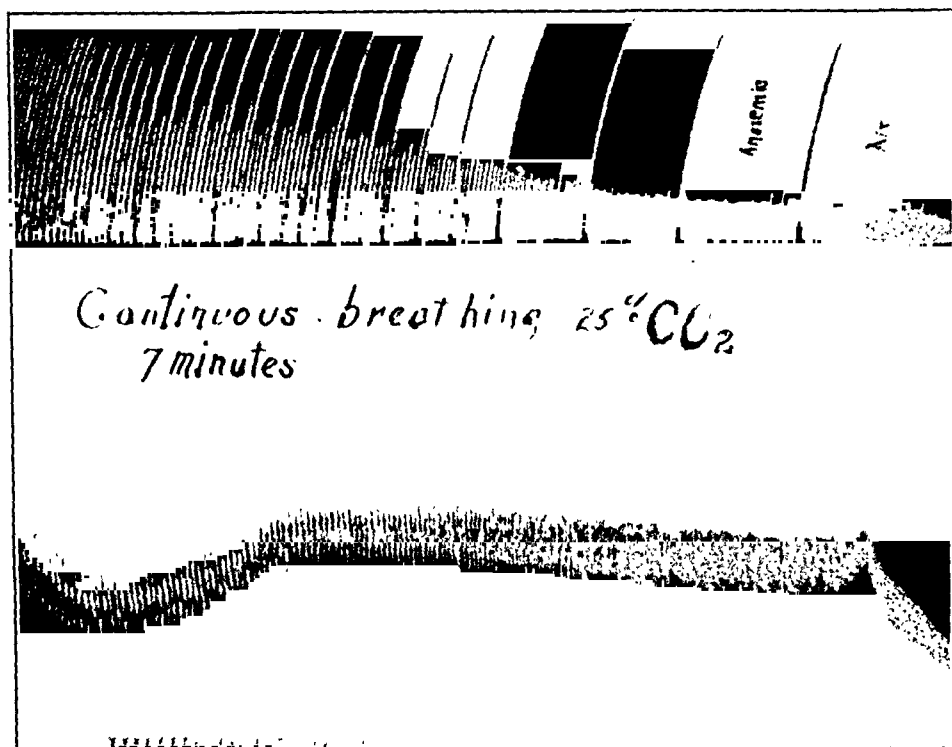


Fig. 4.—Showing the effect of breathing 25 per cent carbon dioxide in oxygen for seven minutes. Marked hyperpnea ensues followed by gasping respiration which soon becomes very shallow. In this experiment air was administered at O, but breathing remained shallow and death occurred six minutes later.

DISCUSSION

DR. JOSEPH KREISELMAN.—During the past ten years many articles have been written on the subject of asphyxia neonatorum, but as far as I know all articles except those of Drs. Eastman, Kane, and myself have recommended carbon dioxide. Yet there is no experimental evidence to prove that carbon dioxide is the agent to use. We do know of recent work, however, contraindicating carbon dioxide in all other forms of asphyxia. This is also true with anesthesia, particularly in the use of such depressant anesthetics as cyclopropane. Respiration ceases when we use carbon dioxide. This has been shown also in New York University where experiments are being done with the barbiturates.

DR. H. P. RAMSEY.—The experimental work offered here has been conducted entirely on animals that have already been breathing and have their respiratory mechanisms functioning, while with the infants who have not breathed another situation is present. Has this difference no bearing on the discussion?

DR. JAMES F. DAVIDSON.—One thing that we are up against in all these problems is the preliminary medication given by the obstetrician. Morphine, for example, is a depressant not only to the mother, but to the child. If the latter is born within an hour or two after the administration of morphine sulphate there is a special problem in getting the infant to breathe.

DR. E. KIRBY SMITH.—There are many other factors in so-called asphyxia neonatorum besides the lack of oxygen. Many things preceding the birth of the infant may depress the respiratory center. Not only the opiates, but perhaps a certain amount of shock may have some bearing upon it.

DR. SOLLIE KATZMAN.—Henderson certainly advocates CO₂, but not to the extent of 25 per cent of carbon dioxide and 75 per cent of oxygen. A 25 per cent mixture of CO₂ is not a resuscitant but an anesthetic and will put the patient to sleep. I am surprised that Dr. Eastman got any of his infants to breathe at all with a 25 per cent mixture.

Dr. Ebersole of the Lahey Clinic in Boston has introduced the use of helium in a mixture of 80 per cent helium and 20 per cent of oxygen. It is used not only in resuscitating infants but also during anesthesia where there is an obstruction. The helium is used because of its lighter density in getting to the lungs and ease of aeration. Helium may be a point to remember in future experiments.

DR. S. M. DODEK.—Some six years ago, working with the Departments of Pharmacology and Obstetrics at Western Reserve, we were using Dr. Kreiselman's apparatus with pure oxygen to resuscitate the newborn, and we had very excellent results. We subsequently switched to the use of pure compressed air for resuscitation of the newborn infant, and we found that every depressed newborn who had no birth injury or atelectasis could be resuscitated within a period of twenty minutes with pure air.

DR. HOWARD KANE.—About ten years ago when the Kreiselman apparatus was being developed, a question arose as to what was the better gas to use. It seemed to us that the babies all had the appearance of having too much CO₂, so we took samples of blood from 100 cords and had them examined quantitatively for CO₂ and oxygen. We divided the babies into three groups: First, those that were born crying; second, those that were born with delayed respiration; third, those that had to be resuscitated. The crying babies had a small amount and the babies needing resuscitation had a large amount of CO₂, which seemed to us to prove that CO₂ was not needed.

DR. NICHOLSON J. EASTMAN.—With regard to Dr. Ramsey's comment, you remember I closed my remarks by saying that it is hazardous to carry over from animal experimentation, particularly in asphyxia neonatorum, any conclusions. I said particularly asphyxia neonatorum because there we have an infant who has not breathed air before. Much as we should like to carry out such experiments in newborn animals, technical difficulties have made that impossible.

deficiency alone, an effect that is particularly undesirable in asphyxia, because the body temperature has already been lowered by vascular collapse.

In the present series of experiments this toxic action of carbon dioxide on protoplasm appears to have manifested itself in several ways: first, by the convulsive, unstable character of the respiration following resuscitation by this gas; second, by the inability of animals which had been resuscitated by carbon dioxide mixtures to withstand repeated asphyxiation; and finally by the lethal effect of this gas when inspired in a concentration of 25 per cent for a long period. As resuscitating agents, these carbon dioxide mixtures showed no points of superiority over pure oxygen. In our hands, then, pure oxygen appeared to be preferable to carbon dioxide as a resuscitating agent in experimental anoxemia. While this conclusion is not necessarily applicable to asphyxia neonatorum, it is in keeping with the view that in that condition also pure oxygen is the preferable gas.

SUMMARY

1. The apnea of experimental anoxemia in animals reduplicates exactly the clinical picture, as well as the blood oxygen levels, of asphyxia neonatorum.

2. When animals are asphyxiated to the stage of apnea, resuscitation is accomplished just as quickly by insufflation with pure oxygen as it is with carbon dioxide mixtures; in the presence of profound asphyxia, pure oxygen is more efficacious than carbon dioxide.

3. Following resuscitation with pure oxygen the restored respiration remains normal in rate, amplitude, and general character, but following resuscitation with carbon dioxide mixtures the respiration tends to be convulsive and irregular; it frequently becomes shallow so that further artificial respiration is needed.

4. If animals are allowed to breathe 25 per cent carbon dioxide in oxygen for 7 to 15 minutes, grave toxic effects are produced which often result in death.

5. In experimental anoxemia pure oxygen is superior to carbon dioxide as a resuscitating agent, a circumstance which is in keeping with the view that pure oxygen is likewise preferable in the treatment of asphyxia neonatorum.

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of 5 to 10 c.c. of air into the ear vein. The abdomen was quickly opened and the uterus excised. After opening the uterus, each fetus was removed with its placenta, which was readily separated from the uterine wall. The umbilical cord was severed close to the body of the fetus and the latter weighed with one or more of its litter mates, after the membranes had been carefully stripped from its body. Only those fetuses which showed active movements after rupture of the membranes and which showed no developmental defects were taken for analysis. In all cases at least two fetuses were taken, one being selected from each uterine horn; at early stages when the fetuses were small, four were selected and combined for analysis. The fetuses, after being carefully washed in a stream of distilled water to remove any adhering debris or amniotic fluid, were finely minced into a large Kjeldahl flask by means of heavy scissors.

Two placentas were also taken for analysis from each of twelve litters. The maternal and fetal portions were separately analyzed in seven of the experiments. Separation of the maternal from the fetal portion was easily and effectually accomplished by gentle traction with forceps. No attempt was made to wash the placentas of the gross blood which they invariably contained. After being weighed on watch crystals, the placentas were similarly minced into Kjeldahl flasks.

As no satisfactory method was available for the estimation of minute quantities of the various decomposition products of the arsphenamines, it was necessary to confine the analyses to the estimation of total arsenic.

The tissues were ashed immediately in a mixture of sulfuric and nitric acids and then analyzed by a modification of the Gutzeit method, which depends upon the liberation of arsine (AsH_3), producing a brown stain upon a paper strip previously sensitized with mercuric bromide (Association of Official Agricultural Chemists, 1931). Estimation of arsenic is made by comparison of the intensity and length of this color stain with standard stains simultaneously prepared from a stock solution of arsenic trioxide (As_2O_3). Accordingly, the readings are expressed in terms of arsenic trioxide.

Since the chemical analysis in each experiment was done jointly on two or more fetuses from the litter, the results represent the average arsenic content as calculated for a single fetus. Similar calculations were made for the placentas.

Duplicate and control determinations showed the analytical methods to be reliable as well as extremely sensitive, serving to detect as little as one-half micromilligram (thousandth of a milligram) of arsenic trioxide. With quantities exceeding 2 micromilligrams, readings were made to the nearest micromilligram. Smaller quantities were estimated to the nearest half-micromilligram. All reagents used in the analytical procedures were arsenic-free, blank controls being run with each set of determinations. Repeated tissue controls upon newborn rabbits were uniformly negative, never showing more than a faint trace of arsenic, too small for estimation. As a further check on the method, it was shown that the arsenic which was recovered by ashing a newborn rabbit a few minutes after an injection of neoarsphenamine into it, agreed remarkably closely with the arsenic content of the injected drug.

The observations are based upon analyses of 44 fetuses and 24 placentas which were obtained from the litters of 24 healthy, multiparous rabbits at various stages of pregnancy from nineteen to thirty-five days. Accurate estimation of the stage of pregnancy was assured, since the animals were isolated in separate cages and mated in the laboratory.

The average period of gestation in the rabbit is normally thirty-two days. In some of the experiments, however, it was desired to prolong pregnancy, inhibition of labor being accomplished by a single intravenous injection of antuitrin-S (Parke, Davis & Co), 1 c.c., twenty-five days after insemination. It is understood that all pregnancies of more than thirty-two days' duration were prolonged in this manner (Snyder, 1934).

The rabbit was selected as a favorable animal for study, because of the structural similarity of its placenta to that of the human being, both being of the hemochorial type (Grosser, 1927).

In studies on the oxygen content of newborn babies' blood, the constant finding in true asphyxia is low oxygen and by definition the constant finding in experimental anoxemia is low oxygen. Other similarities seemed to make it justifiable to carry out this study, and with the reservations that I have mentioned to apply it to asphyxia neonatorum.

Dr. Katzman misunderstood me. We did not administer 25 per cent carbon dioxide to infants, but only to these dogs who showed the usual anesthetic effects. In the bibliography is a reference to a article published by Dr. Yandell Henderson in the *Journal of the American Medical Association* I believe in 1931, in which he states that in ordinary cases of asphyxia neonatorum 7 per cent carbon dioxide is used, but that in severe examples of this condition 25 per cent may be necessary. I took the liberty of using Yandell Henderson's recommendation of 25 per cent in severe cases of this condition.

THE PLACENTAL TRANSMISSION OF NEOARSPHENAMINE IN RELATION TO THE STAGE OF PREGNANCY

WITH SPECIAL REFERENCE TO THE PRENATAL TREATMENT OF SYPHILIS

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THE present investigation is an attempt to measure one aspect of placental function, namely the capacity of the placenta to transmit substances from the mother to the fetus. A single injection of neoarsphenamine was given to rabbits at various stages of pregnancy; after a constant interval of time, quantitative determinations were made of the arsenic content of the fetuses and of the placentas. It was thus possible to determine the rate of arsenic transmission by the placenta at various stages of pregnancy.

A second object of the present experiments was to elucidate the mechanism of the antisypilitic effect upon the fetus of arsenicals administered during pregnancy. It has been a matter of uncertainty whether there is transmitted to the fetus a sufficient concentration of therapeutically active arsenic to influence infection, or whether the placental arsenic is alone effective in prenatal treatment.

METHODS AND MATERIALS

In a typical experiment 2 c.c. of a freshly prepared solution of neoarsphenamine (Merck) were injected into the ear vein of a rabbit, the dilution being made so that the amount injected contained 0.020 gm. of the arsenical per kilogram of body weight. This represents the therapeutic dosage for the rabbit (Kolle; Kolmer, 1926), and although somewhat greater than the corresponding dosage for the human being, is still well within the limits of safety, the therapeutic index for the rabbit being 1:10 (Kolle). In two experiments this dosage was doubled, 0.040 gm. per kilogram of body weight being injected, but in no instance was the injected drug observed to exert any untoward effect upon the normal course of pregnancy, labor, nor any deleterious effect upon the fetuses. All ampoules of neoarsphenamine were from the same batch of manufacture; our analysis showed the arsenic content to be 20 per cent.

Following the administration of the neoarsphenamine, the rabbit was kept at rest for a definite period of time, after which it was rapidly killed by the injection

Two litters were sacrificed for analysis seventy-two hours following injection. The maternal animals were injected at nineteen- and twenty-eight-day stages, respectively, with the same dosage of neoarsphenamine, 0.020 gm. per kilogram of body weight, and determinations were made on 6 fetuses. The nineteen-day fetus was found to contain a trace of arsenic, while in striking contrast to this, the twenty-eight-day fetus contained 14 micromilligrams.

The effect of doubling the dosage of neoarsphenamine, administering 0.040 gm. instead of 0.020 gm. per kilogram of body weight, was observed in four fetuses obtained from two litters sacrificed one hour after injection at twenty-nine days. There was recovered in one litter 2 micromilligrams of arsenic per fetus, and in the other, 3 micromilligrams. In the three rabbits injected with the standard dosage of 0.020 gm. per kilogram at this stage of pregnancy, each of the fetuses contained 2 micromilligrams of arsenic after the same interval following injection. It is thus evident that doubling the amount of the drug which the mother received did not produce a proportionate increase in the placental transmission of it.

Placenta.—The placenta consistently contained a total amount and concentration of arsenic which were considerably greater than those in the fetus. Examination was made in all cases one hour following the injection of the standard dosage of neoarsphenamine, 0.020 gm. per kilogram of maternal body weight. In 24 placentas obtained from 12 litters which included stages from the twenty-seventh to the thirty-fifth day of pregnancy, the arsenic content averaged 71 micromilligrams. The maximum arsenic content of a placenta was 100 micromilligrams; the minimum was 49 micromilligrams. The concentration of arsenic averaged 14 micromilligrams per gram of placenta, ranging between a maximum of 18 and a minimum of 8 micromilligrams per gram.

Separate determinations of the arsenic content of the fetal and maternal portions of the placenta showed that the total amount and concentration of the arsenical were without exception greater in the fetal than in the maternal portion (Table I).

TABLE I. ARSENIC CONTENT OF PLACENTA ONE HOUR AFTER INJECTION OF NEOARSPHENAMINE AT VARIOUS STAGES BETWEEN THE 27TH AND 34TH DAYS OF PREGNANCY

ARSENIC TRIOXIDE IN MICROMILLIGRAMS

	MAXIMUM	MINIMUM	AVERAGE (SERIES OF 14)	CONCENTRATION (As ₂ O ₃ PER GRAM)		
				MAXIMUM	MINIMUM	AVERAGE (SERIES OF 14)
Total placenta	84	49	65	17	8	13
Fetal portion	75	40	56	20	9	15
Maternal portion	12	7	9	11	4	7

In 14 placentas obtained from 7 litters which represented stages of pregnancy from the twenty-seventh to the thirty-fourth day, the average arsenic content was 56 micromilligrams in the fetal portion and 9 micromilligrams in the maternal portion (Table I). The average concentration of arsenic was twice as great in the fetal portion as that in the maternal portion.

The fetal portion, which averaged in this series 73 per cent of the total placental weight, was found to contain 86 per cent of the placental arsenic. The maternal part, on the other hand, representing 27 per cent of the placental mass, averaged only 14 per cent of the total arsenic content.

No correlation could be established between the stage of pregnancy and the arsenic content of the placenta.

DISCUSSION

The foregoing observations represent a quantitative determination of the activity of the placenta at various stages of pregnancy, using as a

OBSERVATIONS

Fetus.—In a series of 24 fetuses obtained from 12 litters which were sacrificed at various stages of pregnancy, there were striking differences in the quantities of arsenic which were recovered from the fetuses upon examination one hour following injection. The arsenic content per fetus varied from none to 8 micromilligrams. When the stage of pregnancy was taken into consideration, it was evident that a definite correlation existed between the age of the fetus and its arsenic content. At twenty-five days no arsenic could be detected in the fetus. At twenty-seven days a small amount, estimated to be $\frac{1}{4}$ micromilligram, was found. From the beginning of the period of viability, that is, twenty-eight days, increasingly larger amounts of arsenic were found in the fetus as pregnancy progressed, the greatest amount in the series, 8 micromilligrams, being recovered at thirty-four days, or two days past term.

When the increase in weight of the fetus was taken into account, it was found that the arsenic content per unit weight of fetus also increased as pregnancy progressed, the curve being roughly parallel to that representing the total arsenic content (Fig. 1).

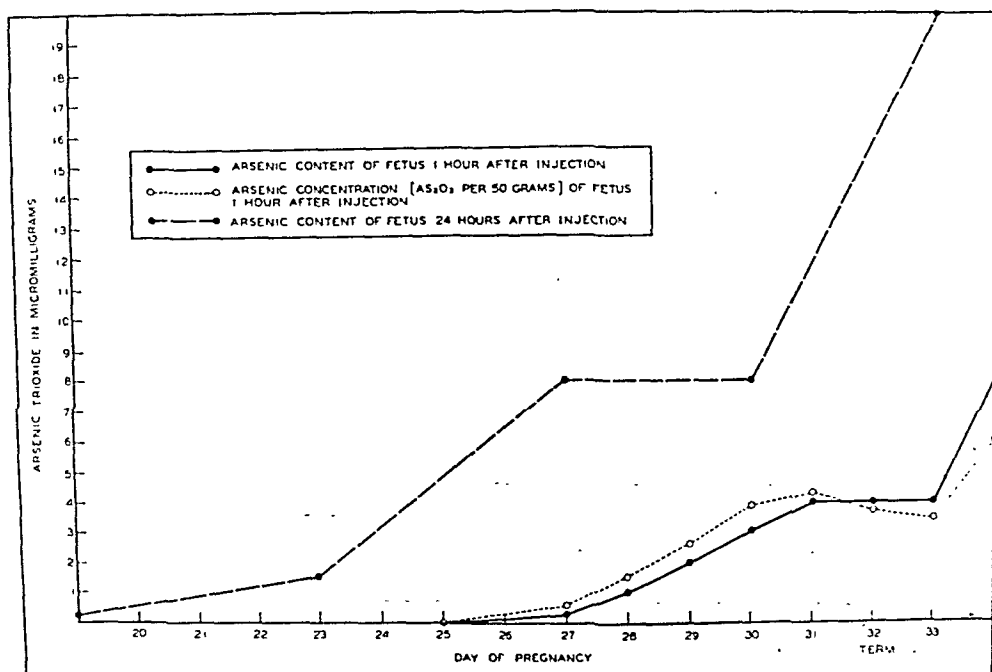


Chart 1.—The rate of transmission of neoarsphenamine from mother to fetus increases as pregnancy progresses. Each dot represents the result of analysis of at least one litter; at the twenty-eight- and the twenty-nine-day stages in the one-hour series, the results are based upon agreement of analyses of two and three litters, respectively. The abscissa denotes the stage of pregnancy at the time of injection.

In a second series of 14 fetuses obtained from 5 litters in which a longer period of time, namely, twenty-four hours, elapsed following injection, it was found likewise that the amount of arsenic in the fetus increased as term was approached. Arsenic was detected at an earlier stage of pregnancy than in the one-hour series, $\frac{1}{4}$ micromilligram being recovered in a fetus at nineteen days. At the opposite extreme, namely, in postmature fetuses examined at thirty-four days, the arsenic content of a single fetus reached the maximum of the series, 20 micromilligrams, as compared with a maximum of 8 micromilligrams recovered one hour after injection at the same stage of pregnancy. At a given stage of pregnancy a larger quantity of arsenic was in the fetus twenty-four hours following injection than after one hour. The arsenic content per unit weight of fetus also increased as pregnancy progressed, the curve of arsenic concentrations being roughly parallel to that representing the total arsenic content after twenty-four hours.

ing increase in the amount of arsenic which is transmitted to the human fetus as term is approached, similar to that which has been demonstrated in the rabbit.

Examination of the placentas revealed that a vastly greater amount of arsenic is retained by this organ than is transmitted to the fetus one hour following injection at full term. The average concentration of arsenic in the placenta was 175 times as great as that in the fetus, and the total arsenic content of the placenta was 18 times as great as that of the fetus.

Gradual liberation to the fetus of the arsenic stored in the placenta is revealed by the higher level of the drug in the fetuses twenty-four hours after injection than after one hour.

In the rabbit the complete separation of the fetal portion of the placenta from the maternal portion is readily accomplished, thus permitting accurate comparison of their respective stores of arsenic. The fetal portion contained, on an average, a total amount of arsenic six times as great, and a concentration twice as great, as that of the maternal portion. Previous investigations of the distribution of arsenic in the human placenta (Dejust and Vignes, 1925; Eastman, 1931) showed similarly a greater retention of the arsenical by the fetal portion, although results in the human being are complicated by the failure to attain complete separation of the two portions of the placenta, as well as by the variations among the specimens with respect to dosage and the time interval which elapsed following injection.

The storage of arsenic in greater concentration in the fetal portion affords an interesting contrast to the distribution of glycogen in the placenta, since glycogen is restricted to the maternal portion (Loveland, Maurer, and Snyder, 1931).

In the placenta, in contrast to the fetus, the variations in the total content and concentration of arsenic were not related to the stage of pregnancy. Similarly, no correlation was noted between placental arsenic, on the one hand, and the size of the litter, weight of the placenta, or total amount of neoarsphenamine injected, on the other. Since no attempt was made to wash the placentas, the unequal amounts of residual blood were taken into consideration as a possible source of the variations. However, the arsenic content of the blood one hour after injection has been shown to be sufficiently low, even when much larger doses of neoarsphenamine are employed (Voegtlin and Thompson, 1923; d'Haenens, 1925; Speert, 1937), so that differences of as much as 1 c.c. in residual placental blood, estimated to be the upper limit of variation, are inadequate to account for significant differences in the data. Probably of greater importance in this regard is the variable degree to which placentas in the later stages of pregnancy show regions of necrosis, infarction, and scarring, structural changes which alter the amount of functional tissue available for arsenic retention.

The present experiments throw light upon the mechanism of the anti-syphilitic effect upon the fetus of prenatal arsenical therapy. Although Underhill and Amatruda denied that placental transmission of the drug to the fetus is sufficiently great to be of importance in therapy, our

measure of placental function the amount of arsenic which is found in the fetus after the injection of the mother with neoarsphenamine. Under conditions standardized with respect to dosage and time interval following administration of the arsenical, there is revealed a progressive increase in the rate of placental transmission of arsenic from mother to fetus as pregnancy approaches termination. The amount of arsenic which passes the placenta within a definite time interval is a function of the stage of pregnancy, being roughly proportional to the age of the fetus.

The present findings are supported by a previous investigation in which the stage of pregnancy was found to be an important factor in the rate of transmission of a substance across the placenta in the opposite direction, that is, from fetus to mother (Lell, Liber and Snyder, 1932). Following the injection of fetuses in the uterus with phenolsulphonphthalein, the rate of excretion of the dye from fetus to mother was found to vary with the stage of pregnancy, but in an inverse direction, the output of the dye progressively decreasing as term was approached. In this investigation, as well as in the present experiments, the rate of placental transmission was governed by a gradient which was related to the stage of pregnancy.

It is clear, therefore, that any investigation of the placental transmission of a substance, be it from mother to fetus or vice versa, must take into consideration the stage of pregnancy as a factor of the first importance. Neglect of this factor and lack of sensitivity of analytical methods may account for the failure of previous investigations (Meyer, 1915; Underhill and Amatruda, 1923) to reveal more than a trace of arsenic transmitted to the fetus, despite the administration of larger amounts of arsenical than those given in the present experiments.

In the human being, Kraul and Bodnar (1926) found that in a series of four pregnant women who had received neoarsphenamine therapy and subsequently expelled fetuses at various stages of pregnancy, there was arsenic in three fetuses which were born in the latter part of pregnancy, but none was present in a fetus extruded at six months. The passage of the drug or some of its decomposition products to the human fetus was also demonstrated by Eastman and Dippel (1933), who recovered small amounts of arsenic from the meconium of newborn infants whose mothers had received antisyphilitic treatment during pregnancy.

The statistical analysis of McKelvey and Turner (1934) has shown that in pregnancy the last trimester is clinically the most important period for arsenical therapy, and that even a few treatments in the last weeks preceding delivery will materially improve the chances for a healthy child. A relatively small amount of arsenical affords the fetus better protection against syphilis when the drug is given late in pregnancy than when it is given only at earlier stages of gestation. In the human being we have been able to discover no data regarding the quantity of arsenic which is transmitted to the fetus at various stages of pregnancy. The increase in therapeutic efficiency of the arsphenamines as pregnancy progresses suggests, however, that there is a correspond-

5. Variations in the arsenic content of the placentas could not be correlated with the stage of pregnancy.

6. Gradual liberation of arsenic from the placenta to the fetus is indicated by the consistent finding of a greater amount of arsenic in the fetus twenty-four hours after injection than after one hour.

7. The concentration of arsenic in the fetus near term approaches the level calculated to be present in the maternal tissues when definite anti-syphilitic effect is exerted.

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THE DIET OF THE PREGNANT WOMAN*

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STUDIES of the basal metabolism of pregnant women have shown that it tends to fall very slightly during the first months, being, according to Root and Root, 1.5 per cent below the Harris-Benedict standard for a woman of the same height and weight in the fifteenth week. Thereafter, it steadily rises until a few days before delivery, when it is about 23 per cent above that of five months earlier. The gain in weight during pregnancy approximates 14 per cent. An increase in metabolic rate corresponding to increase in weight would result in an increase in metabolism of only 5 per cent, instead of the observed 23 per cent. It is evident, therefore, that the fetal tissues and their adnexa have a higher specific metabolism per unit of weight than that of the unincumbered woman.

All authorities are agreed that the pregnant woman requires for her nutrition nothing other than those nutrients which she requires in the nonpregnant state, but that she needs more of everything, but particularly more energy, protein, calcium, phosphorus, iron, and

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findings indicate that in the fetus there is a concentration of arsenic which is comparable to that in the maternal tissues. It may be inferred, therefore, that there is sufficient arsenic in the fetus to be an effective therapeutic agent. The arsenic concentration of the maternal tissues was calculated from data obtained by Voegtlin and Thompson (1923). In rats injected with a considerably larger dosage of neoarsphenamine than that given in the present experiments, these authors found an average excretion of 88 per cent of the administered arsenic in twenty-four hours. If one accepts this rate of excretion as applying for rabbits, the concentration in the maternal tissues twenty-four hours following injection is only twice as great as the maximal arsenic concentration in our series of fetuses. The placenta shows an average arsenic concentration 18 times as great as that of the maternal tissues.

In summary, there is evidence that a single injection of a therapeutic dose of neoarsphenamine administered near term results in a concentration of arsenic in the fetus and in the placenta, which is sufficient to exert an antisiphilitic effect. In explanation of the greater therapeutic efficiency of a given amount of arsenical, as measured by its ability to insure the birth of a nonsiphilitic offspring, when the drug is administered during the last trimester of pregnancy in contrast to earlier stages, it may be pointed out that as term is approached increasingly larger amounts of arsenic are transmitted to the rabbit fetus, as demonstrated in the present experiments.

It is interesting to note that the stage of pregnancy at which arsenic is first transmitted across the placenta of the rabbit, namely, about the beginning of the latter half of pregnancy, corresponds to the earliest stage of gestation in the human being at which the *Treponema pallidum* is found in the fetus (Hoffmann, 1936). The failure of substances as diverse as a chemical compound and a living microorganism to be transmitted to the fetus during early pregnancy, in contrast to later stages, illustrates the profound alteration in placental function which occurs as pregnancy progresses.

CONCLUSIONS

1. Placental function, as measured by the capacity of the placenta to transmit arsenic from mother to fetus, varies with the stage of pregnancy, the rate of transmission increasing as pregnancy progresses.

2. In a series of rabbit fetuses examined one hour following injection of the mother with neoarsphenamine, no arsenic was detected until the period of viability was approached; in a second series, examined twenty-four hours following injection, arsenic was found in the fetus as early as the beginning of the latter half of pregnancy.

3. The placenta contained much more arsenic than the fetus; the average arsenic content of the placenta was 18 times, and the arsenic concentration 175 times, as great as that of a fetus at full term one hour following injection.

4. The fetal portion of the placenta contained 6 times as much arsenic as did the maternal portion; the concentration of arsenic was only twice as great in the fetal as in the maternal portion.

suffered anxiety at one period during pregnancy went into negative calcium balance at that time. It is well known that vitamin D is extremely important in conditioning the body to utilize both of these elements, and more particularly phosphorus. If the diet of the pregnant woman contains sufficient milk and green vegetables, she will secure sufficient of both of these elements. She will not, however, utilize these properly, unless the remainder of her diet be properly constituted, as will be presently shown.

Iron.—Our views concerning the utilization of iron in nutrition have undergone significant changes in recent years. There is abundant evidence that deficiency of this element is widespread. I shall not discuss anemias other than that form for which idiopathic hypochromic anemia has become the term of choice. This is a simple secondary anemia in which the reduction in hemoglobin greatly exceeds that of the red cells. It is likely to occur in any individual who suffers from gastric anacidity, and is frequently encountered during pregnancy. Strauss (1934 and 1936) has given an excellent discussion of this condition. He points out that gastric digestive defects, in association with fetal demands for iron, may be the cause of this anemia, and that it can be relieved or avoided by the administration of generous amounts of iron. He recommends 0.5 gm. daily of ferrous sulfate for this purpose.

In this connection I should mention the importance of selecting the best form of iron compounds for therapeutic use. Simmonds, Becker, and McCollum (1927) showed that the inclusion of 0.2 per cent of ferrous sulfate in the diet of the rat causes almost, if not quite, complete destruction of vitamin A. When this salt is added to butter fat or cod liver oil, these fats very quickly become rancid, and the destruction of vitamin A is catalyzed. No such effect is produced by ferric citrate, hence, I would suggest that a ferric salt be used instead of a ferrous salt. Elvehjem and co-workers (1933) have recommended ferric pyrophosphate as a salt having almost ideal properties for therapeutic purposes, since it is readily absorbed, and is the least astringent of iron salts commonly available.

Until recently it was believed that the total iron content of ordinary foods is available for utilization by the body. The introduction of the new dipyriddy reagent by Hill, which differentiates between the so-called "hematin" iron and other forms of iron, and extensive studies at the University of Wisconsin, by Elvehjem (1933), has brought to light the fact that only about 50 per cent of the iron in such common foods as wheat, oats, and yeast, is available physiologically. The body's daily requirement for iron has for years been assumed to be about 15 mg. for the unincumbered adult, and for the pregnant woman the figure has been set at 20 mg. or above. But since the iron of foods is by no means all available, the actual requirement for iron becomes problematical.

Further light has been thrown on this subject by recent researches. Mettier (1930) found that certain anemic patients did not respond to iron therapy, but did so readily when iron was provided along with a

the vitamins. The more recent contributions to our knowledge of the nutrient requirements of the expectant mother, and considerations affecting her utilization of food substances, present some interesting viewpoints of great practical importance. They reveal certain aspects of maternal nutrition which require special attention, and errors which may have grave consequences, but which may, in most instances, be avoided by wise management.

Provided no conditions arise which interfere with digestion and absorption there is no special problem in pregnancy arising in relation to the protein moiety of the diet. The proteins should have high biologic value, and this is easily attainable by the inclusion of suitable amounts of milk and meats, since the proteins of these foods supplement well those of cereals and other vegetable foods and increase the utilization of the latter. When pregnancy is complicated by frequent vomiting, the amino acid needs of the woman will not be satisfactorily met, however satisfactory may be the quality or quantity of her food proteins. The same may safely be said regarding any other dietary essential. In calling your attention to certain experimental and clinical observations bearing on the nutrition of the pregnant woman, my objective is to bring together for your consideration ideas which are new and which further study may show to require revision or modification, but which have sufficient basis for confidence, both in animal experiments and clinical observations, to warrant careful attention by clinicians.

THE MINERAL ELEMENTS

Calcium and Phosphorus.—Macy and her co-workers (1930) made quantitative studies on the calcium and phosphorus balances of three women, and found that one experienced considerable losses of calcium at the twenty-sixth and thirtieth weeks of gestation; another at the fourteenth week, and a third at the thirtieth and thirty-fourth week, although their usual home diets were abundant in all known food essentials. Phosphorus retention appears from their data to have been more satisfactory than that of calcium. Sherman (1932) and Schmidt and Greenberg (1935) estimate the average daily calcium intake of American women to be 0.063 gm. The average daily calcium intake of the women studied by Macey and co-workers was 1.735, 1.97, and 2.09 gm., and of phosphorus, 2.25, 1.70, and 2.46 gm., respectively. The ratio of Ca:P in these diets was 1:1.3, 1:0.86, and 1:1.17. In absolute amounts of these elements, these diets were undoubtedly sufficient. If we may judge of human requirements by those of the rat, it appears from the studies of Cox and Imboden (1935) that a ratio of Ca:P of 1 is near the optimum, when the calcium level is 0.49 per cent of the diet. They tentatively place the calcium requirement of the human adult at 1.37 gm. An excess of phosphorus is better tolerated than an excess of calcium.

There are several factors which influence calcium and phosphorus metabolism. One of these is worry. Macy found that a woman who

4. An increase in the death rate from goiter as shown by the Board of Health statistics reached its peak in the second year after the introduction of iodized salt.

5. There was no increase in hyperthyroidism, excepting in the nodular or adenomatous group.

6. The number of operations for toxic diffuse and toxic nodular goiter has rapidly and steadily decreased after the apex of the second year increase had been reached.

7. The incidence of endemic goiter or enlarged thyroid has been reduced almost to nil since iodized salt has been so widely used.

8. We now see no cases which show the slightest ill effects from the use of iodized salt.

9. Toxic nodular goiter and toxic diffuse goiter are less likely to occur when there has been no previous enlargement of the thyroid (endemic goiter); at least this would seem a safe conclusion based on our experience."

The Vitamins.—Vitamin A is now a familiar substance, having been prepared in the crystalline state by Holmes, and also as its precursor, carotene, the yellow pigment of many yellow fruits and vegetables. A deficiency of this vitamin causes keratinization of epithelial tissues throughout the body. Keratinized epithelium tends to desquamate and form foreign bodies at any site where it occurs. Relatively severe depletion of the body of this nutrient causes depletion of the retina of visual purple, with consequent loss of acuity of vision in subdued light; a high incidence of cystitis and of kidney stones; invasion of the respiratory tract by microorganisms which produce purulent accumulations, and cause a high mortality from respiratory infections.

In human subjects such degrees of depletion are common in certain parts of the world, but are rare in America. Much confusion now exists on the point of the extent and seriousness of vitamin A deficiency here. The test for disadaptation of the eyes as a sign of incipient vitamin A deficiency, introduced by Jeans, has all but been discredited by other workers. All that can be safely said at present is that vitamin A deficiency is not uncommon in man in certain places, and that even incipient keratinization of epithelium should, by all that we know, be a menace to health. Mason's observation that senile vaginitis responds to vitamin A therapy, points strongly to the belief that even the American diet may in many cases induce deficiency. The studies on student groups and industrial groups, in which a dietary supplement was given one group, and an unsupplemented group served as controls, seem to establish, that whereas the provision of an abundance of vitamin does not reduce the number of colds per person per year, it does reduce both their severity and duration. The ease with which it can be demonstrated that the enamel of the teeth can be made hypoplastic in experimental animals by a degree of deficiency of vitamin A which does not reveal itself in other symptomatology, further supports this conclusion.

diet containing an abundance of fresh fruits and vegetables. In fact the anemia accompanying scurvy is, he states, relieved by such a diet. This would seem to indicate that ascorbic acid is in some way necessary for iron utilization. That this may be the case is shown by a study reported by Dunlop and Scarborough (1935) on a scorbutic man. He had eaten bread, syrup, margarine, corned beef or smoked sausage, cheese, and tea made with sugar and canned milk, during a year and a half. During this period he had taken no fresh vegetable foods, potatoes or fresh milk. His iron intake was estimated at 10 mg. per day, or two-thirds the assumed requirement. He was kept on his usual diet and given 60 mg. daily of ascorbic acid. Blood corpuscles increased during seventeen days from 2,050,000 to 4,226,000, and the hemoglobin from 45 to 77 per cent. After this he was continued on his usual diet, but no more ascorbic acid was administered, yet in eleven weeks the corpuscles increased to 5,600,000, and the hemoglobin to 100 per cent. They conclude that vitamin C deficiency may be a factor contributing to the development of anemia, even in the absence of clinical signs of scurvy. The studies referred to point strongly to undernutrition as respects ascorbic acid, as a possible cause of anemia in pregnant women. Clinicians should extend our knowledge in this direction.

Iodine.—The excellent studies of Marine, Kimball, McClure, and Olin, in Michigan and Ohio, which are endemic goiter regions, have shown beyond question the importance of keeping the thyroid glands of pregnant and lactating women saturated with iodine. Writing in 1935, McClure, of the Henry Ford Hospital, said:

“In Michigan iodized salt was introduced through the grocery stores by the efforts of the Pediatric Section of the Michigan State Medical Society in 1924. The results in Detroit and Southern Michigan which we have studied have been astounding, as viewed from the number of enlarged thyroids among the school children and also the number of patients coming to operation for the three types of goiter—colloid, adenomatous, and hyperplastic. In 1924 the survey of Kimball in different parts of Michigan showed a very high incidence which has always been endemic here. In Detroit it was not as high as in other parts of the states, but even here there was an incidence of 35 per cent of enlarged thyroids in the school children. In the eleven years that have passed, this incidence has gradually decreased until now less than 1 per cent of our school children have enlarged thyroids. After two years with the use of this salt the number of goiter operations in the seven largest hospitals in Southern Michigan began to decline, but the total of all operations showed but little change. The following conclusions are reached from our studies here:

1. Iodized salt as used in Michigan did, at first, apparently increase the number of thyroid operations.
2. The increase was in the nodular goiter or adenomatous group, and, we believe, the iodized salt may have activated a group of quiescent adenomas, producing toxic goiter symptoms.
3. The increase reached its peak in the second year after the introduction of the iodized salt.

with. Ascorbic acid is likewise closely associated with the formation of complement in the blood, and the complement content falls a considerable time before signs of qualitative malnutrition are visible. King and his associates have shown that in guinea pigs with low ascorbic acid reserves, but showing no signs of scurvy, the injury which is caused by the injection of half of a minimum lethal dose of diphtheria toxin, or other bacterial poison, is extremely great as compared with animals whose reserves are high. Several other investigators substantiate this fact. Cotti and Larizza (1936) found that the provision of ascorbic acid reduces the blood coagulation time, a matter of great importance to the obstetrician.

Vitamin D.—Vitamin D was discovered in investigations made to determine the cause of rickets, for which condition it is a specific remedy. It maintains at the normal level the inorganic phosphate content of the blood, and also plays a role in maintaining normal calcium metabolism. In recent years vitamin D therapy has been employed therapeutically in a variety of conditions far removed from rickets. These cannot be reviewed here, but attention must be called to the view of Weld, that vitamin D is of even greater importance in maintaining normal capillary resistance than is vitamin C. The observations of Richardson (1934) deserve special mention.

Richardson reported a study of the effect of viosterol during pregnancy on the duration of labor, which should be extended by other obstetricians as soon as possible. The combined duration of labor of 132 primiparous patients who had taken viosterol during pregnancy, totaled 792 hours, or an average of six hours per patient, which, he states, is about one-third the duration of the first normal labor. In his practice the combined duration of labor in 63 primiparous patients who were not given the vitamin totaled 1,197 hours, an average duration of nineteen hours. In a series of multiparous patients who received viosterol during pregnancy, who were not compared with a series of untreated controls, the average duration of labor was 3.5 hours.

Wilder and Howell point out that the majority of human patients with parathyroid enlargement occur in the northern part of the United States, where there is a deficiency of sunshine. The action of ultraviolet rays upon the skin causes the formation of one of the forms of vitamin D. Several investigators have described the extraordinary enlargement of the parathyroid glands in chickens which are deprived of vitamin D and of sunlight. The significance of the parathyroids, in the maintenance of normal calcium metabolism and the onset of tetany, when there is a deficiency of the parathyroid hormone, lends great weight to the suggestion that a satisfactory supply of vitamin D may be of profound significance to the health of the pregnant woman.

Milk Fever.—The tetanic seizures characteristic of so-called milk fever in cows, and of "lambling sickness" in ewes, is now well known to be due to hypocalcemia, and is the analogue of tetany in infants brought about by low blood calcium. It is prevented by feeding a

Vitamin B₁ (Thiamin).—There is much evidence that deficiency of thiamin is widespread among American people to a degree which brings about a borderline state of malnutrition as respects this factor. Cowgill (1934) after an extensive study of the thiamin content of many dietaries, recommends to physicians the consideration of thiamin therapy in gastrointestinal disorders, heart disorders, various neurologic conditions, anemias, infant nutrition, anorexia, restriction of growth, and in conditions of heightened metabolism.

Since anorexia is the earliest symptom of thiamin deficiency, voluntary restriction of food consumption is likely to occur, as has been pointed out by Minot, Strauss and others. Strauss and McDonald (1933) appear to have afforded convincing proof that the multiple neuritis of pregnancy is not the result of some occult toxemia, but is due to thiamin deficiency. Women who vomit during pregnancy establish a vicious circle owing to impairment of digestion and absorption, even when the diet which is available is adequate. Berkwitz and Lufkin (1932) have reviewed the literature relating to 52 cases of polyneuritis of pregnancy and conclude: "The clinical and pathological picture of the nerve changes in pregnancy is the same as that resulting from alcoholism, infectious conditions, and diet deficiency disturbances such as beri-beri, and pellagra . . ." Since it is well established that thiamin plays a role in carbohydrate metabolism, and that in deficiency of this vitamin, pyruvic acid cannot be further transformed, and accumulates in the tissues, the suggestion of Plass and Mengert (1933), that the recent tendency to force a high carbohydrate diet on patients with vomiting of pregnancy would seem to increase the risk of producing vitamin deficiency, should be kept in mind. Thiamin is used up in carbohydrate metabolism, and the higher the intake of this moiety of the diet, the greater is the requirement for this substance. It appears probable that the convulsions which occur in thiamin deficiency are due to the accumulation of pyruvic acid in the brain. The significant fact which emerges from the observations cited, on the effects of thiamin deficiency, and of vomiting in pregnancy, is that prevention should be the watchword, and that all women should be educated to understand the importance of taking, before pregnancy occurs, and throughout gestation, a diet optimal in composition, so that the reserves of all the vitamins shall be high. It is suggested that a sound policy is the supplementing of the woman's diet at the outset of pregnancy, with yeast, wheat germ, yeast concentrates, such as Vegex or Marmite, or with appropriate doses of the crystalline vitamin, which is now available at relatively low cost.

Vitamin C (Ascorbic Acid).—It is not desirable here to attempt a review of the pathology of scurvy and of subclinical scurvy. It is well established by the work of Hojer, Wolbach, King and others, that deficiency of ascorbic acid impairs the faculty of the endothelial cells to produce and maintain intracellular matrix, and that hemorrhage is due to this impairment. Ascorbic acid has been clearly shown to play a role in one or more oxidation-reduction systems in the tissues, and when the tissue stores are reduced, oxidative processes are interfered

DISCUSSION

DR. A. T. MILHORAT (by invitation).—The need for increased amounts of nutrients during pregnancy is suggested by the increased respiratory metabolism of the expectant mother and the requirements for growth of the fetus. This increase in the total respiratory metabolism, as has been shown, is greater than the increase in body weight. We know from the studies of Carpenter and Murlin (*Arch. Int. Med.* 7: 184, 1911) that the basal metabolism of the expectant mother just before delivery is the same as that of both mother and child just after parturition. The increase in the surface area of the pregnant woman is much smaller than is the increase in her metabolism. Since the heat of the organism must be dissipated through this surface, the relatively greater increase in the total metabolism will result in a rise in the skin temperature. This would explain the feeling of warmth which many pregnant women experience, and their ability to withstand low environmental temperatures with comfort.

The need for increased amounts of calcium and phosphorus during pregnancy is evident. Many normal persons have intakes of these minerals that are barely adequate. Hence, during pregnancy, with its extra demands, the intake is likely to be deficient unless more calcium and phosphorus are ingested.

Dr. McCollum has emphasized, very wisely, the need for increased amounts of vitamin B in instances where large amounts of carbohydrates are given. In women suffering from prolonged emesis, the ingestion and absorption of vitamin B are likely to be impaired. The administration of large amounts of carbohydrates will increase further the needs of a patient whose requirements due to her pregnancy are already great, but whose intake of the vitamin is deficient. The appearance of polyneuritis in these patients should be watched for carefully. It is well to remember that the subjective symptoms of the patient, namely, numbness and tingling of the fingers or toes, appear much earlier and therefore are more valuable for making a diagnosis of polyneuritis than are the findings of sensory defects on neurologic examination. The development of numbness and tingling in such patients should suggest the diagnosis of polyneuritis, and the parenteral administration of vitamin B should be considered.

The tachycardia often observed in patients with gestational polyneuritis may in many instances be due to the same factors as in beriberi. Weiss and Wilkins (*J. A. M. A.* 109: 786, 1937) have shown that the so-called beriberi heart is not uncommon among persons whose diet has been deficient in vitamin B. How often this occurs in pregnancy I do not know, but the likelihood of its occurrence should be borne in mind.

One result of a deficiency of iron easily demonstrated, is the development of a hypochromic anemia. However, another result, that of an inadequate reserve of iron in the infant, is more obscure in its manifestations. Infants born of mothers whose intake of iron had been deficient usually have no anemia at birth but develop anemia within a year unless iron is administered.

The position of the proteins in the dietary management of the expectant mother is still somewhat obscure, but it is likely that more attention will be paid to these important foodstuffs as time goes on. The facts as given in the medical literature at present are these. During pregnancy there is a positive nitrogen balance. Furthermore, the retention of nitrogen during pregnancy is greater than that required for the fetus and adnexa. Under favorable circumstances, therefore, pregnancy is a period of nitrogen acquisition for the mother. For several years I have been interested in the problem of the protein metabolism during fasting and in pregnancy. It appeared of interest to know what influence pregnancy would have on the output of nitrogen during the fasting state. Would the pregnant organism in its need for nitrogen be able to manage its protein budget so that less nitrogen would be excreted? The results surprised me. During pregnancy the nitrogen excretion of the fasting bitch was at least 50 per cent higher per kilogram of body weight than during the nonpregnant state. Therefore, fasting during pregnancy represents a period of excessive destruction of the maternal proteins. A likely explanation is this: The protein molecule cannot be transported as such from the maternal to the

ration sufficiently rich in calcium, and by nutritional management which safeguards the body mechanisms associated with calcium metabolism. It occurs in animals at the outset of lactation, or during early lactation, for the reason that there is then an enormous output of calcium in the milk. If the body's reserves of this element, and the amount in the food are low, the blood calcium falls to the tetany level. The condition responds readily, in most areas, to the injection of calcium gluconate, and is prevented by a high calcium ration. Vitamin D would also be of importance. In a few areas where the soils are deficient in magnesium, the so-called "grass tetany" occurs, which is due to low blood magnesium.

An analogous condition appears to occur in certain women, although the disease has not been studied effectively in human patients. These conditions are mentioned here because they suggest a field of investigation for obstetricians.

In this brief discussion I have attempted to call attention to the more important conditions in which obstetricians are interested, in which the state of nutrition of the expectant mother may be safeguarded by careful attention to the diet. In all normal cases, her nutrition will be adequately met, provided she takes a diet built up around sufficient amounts of what I have called the protective foods. These are milk, green and yellow vegetables, fresh, uncooked fruits, and a moderate consumption of meats. It is not necessary here to particularize as to the special properties of these foods, and their supplementary relations. It is believed that in many instances the expectant mother suffers in health because of too great restriction of her diet to refined cereal foods, manufactured dry food products such as are offered in great numbers in stores, the fats of which are often somewhat rancid, and of sugar. The specific relations which have been mentioned between depletion of the body in respect to particular nutrients, and specific symptoms frequently encountered, are called to attention as evidence that the diet of the pregnant woman in America requires the attention of her physician, and that effective dietetic management should be given to these women as a feature of obstetric practice.

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paresis in cattle at first consisted in the use of a pump to the udder, stopping the excretion of milk; later by giving glucose solution intravenously. Parturient paresis was noted particularly in cattle that were secreting large amounts of lactose, or milk.

I cannot fully agree with Dr. Milhorat on the subject of nitrogen metabolism, although, it is possible that by his recent work he can disprove some of the older views. Hoffström and Bar have shown that in the first third of pregnancy there is a negative nitrogen balance. Bar tried to show that the vomiting of pregnancy, particularly the gastrointestinal upsets observed in dogs, is associated with a nitrogen negative balance. In the second half of pregnancy there is a positive balance. One often sees a pregnant woman, who has been starved and whose weight at term is less than her nonpregnant weight, and yet the offspring is of normal weight.

Another of the important points mentioned by Dr. McCollum was the use of vitamin B₁ in the utilization of carbohydrate, and certainly in our treatment of the vomiting of pregnancy. It is quite conceivable that we could get better results if we paid attention not only to the glucose therapy advocated by Titus and others, but also to the importance of this second factor, namely, vitamin B in the utilization of sugar.

DR. MCCOLLUM (closing).—Dr. Beck asked me a question on which we have only a very limited basis for formulating an answer. The only studies with which I am familiar on the question as to whether a creature eats more of something that it does not need in order to get enough of something it does need, were made about twenty years ago by Osborne and several others. They concluded at that time that experimental animals eat for energy, and that when their energy requirement is satisfied, they stop, even though they need something they do not have in sufficient amount.

The point was raised that it might be hazardous to give women vitamin D during pregnancy. The difference between the therapeutic dose of vitamin D is less than the dose which has been demonstrated to produce toxic effect by many thousand times. The prophylactic dose for infants and children is four hundred international units a day, the equivalent of one teaspoonful of cod liver oil, which would be safe.

In regard to milk fever, I have the impression that there were cures of this condition by the use of calcium salts other than gluconate. In the dose which is given to an animal weighing perhaps 1,000 pounds, it seems inconceivable that the amount of carbohydrate equivalent in gluconic acid would go far in restoring low blood sugar. I think that is a blood calcium deficiency.

Mohr, Harold: The Pathogenicity of the *Trichomonas Vaginalis*, Ztschr. f. Geburtsh. u. Gynäk. 115: 115, 1937.

Mohr found that 55.2 per cent of women with a normal vaginal mucosa were trichomonas carriers. None of these women had any symptoms. On the other hand, 29 per cent of the women examined had typical trichomonas discharge, itching, etc., but were found to be free of trichomonads. This, to the author, was adequate proof that there is no specific pathogenicity. He found that there are no specific bacteria accompanying the organism. The *Trichomonas vaginalis* does not ferment dextrose and causes no change in the glycogen contents of the mucosa. The organisms will survive a pH of 4.0-7.0; they were found in a pH of 5.2-5.8 in 65 per cent of the cases.

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fetal structures. It must be broken down into the amino acids and resynthesized into the fetal proteins. The composition of the fetal proteins, however, is different from that of the maternal proteins; different combinations of the nondispensable amino acids are required. Hence, to supply the necessary amounts of the nondispensable amino acids, more maternal tissue is broken down than is used in the actual synthesis of the fetal proteins. The excess portion of the protein is catabolized, and the nitrogen is excreted in the urine.

Furthermore, animals which were able to withstand repeated fasts of thirty to forty days during the nonpregnant state without harmful effects, did poorly when fasted during pregnancy. Within six or ten days the fasting pregnant animal became nauseated, lethargic and weak. Often delivery was premature, with a high mortality among the newborn. Animals previously fed on highly nutritious diets withstood the fast better than those whose previous diet had been adequate but not especially rich in proteins and vitamins. These findings suggest the need for adequate amounts of proteins of high biologic value during pregnancy. Moreover, it would appear that protein deprivation in this condition very likely will have harmful effect.

In contrast, simple substances such as calcium and phosphorus are readily transferred from the maternal to the fetal tissues. This transfer is economically accomplished and no increased amounts of these minerals are lost in the excreta.

While the average normal woman might be able to go through the reproductive cycle without particular attention to the dietary demands, it is likely that skillful dietary management often is of value to the expectant mother in whom complications are likely to arise. The early months of pregnancy so often associated with vomiting and nausea are frequently a period of inadequate intake of dietary essentials. It is during the next few months, which represent the so-called silent period and which precede the months during which complications are most likely to occur, that the diet can be carefully regulated. The avoidance of any dietary deficiency, however slight, and the adequate storage of all essentials that the body can store might prevent the occurrence of a condition which would precipitate a more serious complication. Moreover, should a complication arise it is possible that the prognosis will be influenced by the previous dietary management of the expectant mother.

DR. ALFRED C. BECK.—For a number of years I have been trying to do some of the things which Dr. McCollum's presentation indicates. By giving a more balanced diet and, particularly, one in which the vitamins and minerals are ample, I believe that my patients have been freer from that condition which we call toxemia than they formerly were. Perhaps, it may be shown that the symptoms of the so-called toxemias are in reality evidences of a deficiency disease.

We all know that pregnant women have enormous appetites and that they overeat and usually gain excessively in weight. In this connection, I would like to ask Dr. McCollum if the tendency to overeat is due to an attempt on the part of Nature to satisfy the requirements of pregnancy by taking larger and larger quantities of highly refined articles of the ordinary diet which are deficient in some of the rarer but necessary elements.

DR. HENRICUS J. STANDER.—A great deal has appeared in the literature on the value of vitamin D in the utilization of calcium. As to whether there may be an excessive deposition of calcium in the fetal bones is an important question and there is some recent evidence in its favor. If this is so, it is possible that too much calcium may do harm, and particularly is that true of viosterol, vitamin D, in the utilization of calcium. I think that we should be a little hesitant about experimenting with the object in view of decreasing the period of labor by the use of vitamin D.

In the reference to milk fever, I think Dr. McCollum had in mind what is known as "parturient paresis" in cattle. Harding, Murphy and Downs of Toronto have shown that parturient paresis is due to a deficiency of glucose or in other words, to a hypoglycemia, rather than to a calcium deficiency. The cure of parturient

ceptable areas as a control. The experiments have been in progress approximately one year. Readings were taken on every individual daily, every second day, or every third day.

The test is readily and simply performed. The suction chamber is applied to the given area for an arbitrarily chosen time of exactly thirty seconds. The final reading is taken when three, and only three, small punctate capillary hemorrhages are produced.

In this work no attempt has been made to determine and correlate all of the numerous associated or related factors, such as blood pressure readings, skin temperatures, seasons of the year, meteorologic rhythm, repeated blood and platelet counts, capillary pressures as determined directly, blood analyses for female sex hormones, epinephrine, cholesterol, carbon dioxide, etc. I realize that many significant

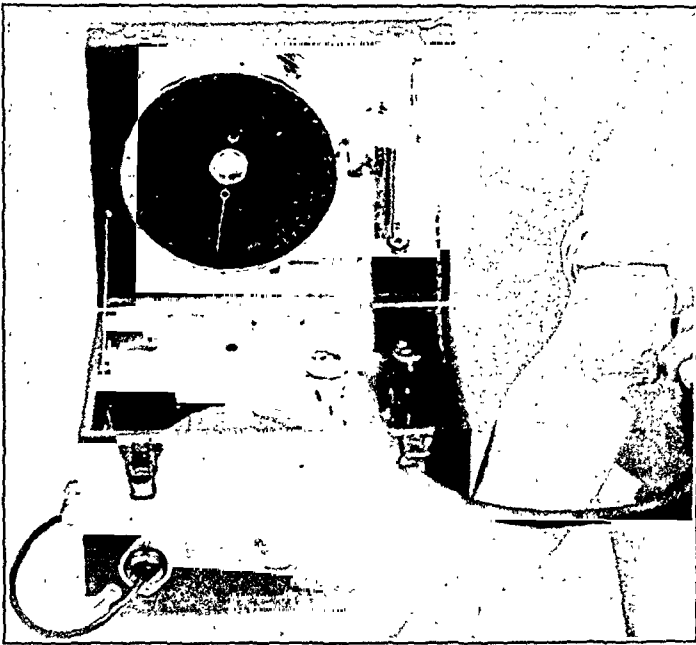


Fig. 1.—The Cutter-Johnson instrument is accurate and readily used clinically. Any desired negative pressure can be obtained and maintained. The site for the test and the method of application are indicated.

rhythmic changes do occur in the body. This paper is limited strictly to but one, the rhythmic changes in the skin capillaries as observed experimentally.

THE SUBJECTS

The total number of female subjects studied was 55. All were normal, healthy, working girls ranging in age from nineteen to fifty years. The menstrual cycles were normal in 40. The normal menstrual cycle has recently been demonstrated to have a wider range of variability than was formerly considered possible. Edward Allen (1933), Engle and Shelesnyak (1934), and others, including excellent summaries by Hartman (1936), Bartelmez (1937), and Ehrenfest (1937), have indicated that the normal cycle may vary four to seven days from the usually accepted normal of twenty-eight days.

Fifteen subjects had abnormal menstrual cycles. They were classified as functional amenorrhea; postclimacteric amenorrhea; amenorrhea resulting from hysterectomy; amenorrhea associated with pregnancy; and functional uterine bleeding.

RHYTHMIC CHANGES IN THE SKIN CAPILLARIES AND THEIR RELATION TO MENSTRUATION*

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INTRODUCTION

THIS present study was undertaken to determine the peripheral vascular changes, particularly those in the skin capillaries, in association with the menstrual rhythm, which is fundamentally a vascular phenomenon. The investigation of the peripheral vascular system was carried out by means of the production of capillary hemorrhages. Petechial or capillary hemorrhage has been studied with respect to many diseases and conditions. H. W. Jones and Tocantins in 1933 presented an historical account of the methods employed. As they stated, Koch in 1889 first tested the capillary resistance by means of intradermal punctures with a needle. The well-known tourniquet test and similar tests were suggested by Weill, Rumpel and Leede, and Frugoni and Guigni in 1911. Jones and Tocantins (1933) described another method of studying capillary hemorrhage, namely, the "flicking" test. The first suction method of testing capillary hemorrhage was described by Hecht (1907).

METHODS

The suction or negative pressure method used in the present experiments is based upon the application of a degree of vacuum adequate to produce capillary hemorrhage in the skin. The instrument was devised by Cutter and Johnson (1935) and has been called a capillary hemorrhage instrument (Fig. 1). This instrument is most satisfactory because frequent and accurate measurements can be made. It is readily adapted to clinical use since it is portable. Any desired negative pressure can be produced down to approximately 1 mm. of absolute vacuum as indicated by Cutter and Johnson (1935). The desired pressure can be maintained at any level. The calibration is such that the negative pressure can be read similarly to barometric pressure, or as done in these experiments, from barometric pressure down to vacuum. Compensation has been made for the pulsatile effect of the pump and the changes which might occur upon application of the measuring chamber and upon opening the stopcock. The small aperture permits one to make numerous tests at one time in a small area.

The skin areas that are the most suitable from the standpoint of constant number and development of the capillaries are the cubital spaces and the infraclavicular regions. In order to obtain the most uniform results only one of these spaces was used during the experiment. In every instance multiple readings were taken at the same time in the same general area. Frequently tests were made in the other ac-

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SUBJECT 2.—Subject 2 is 27 years old. She is 5 feet, 4 inches tall and weighs 125 pounds. Menstruation began with a profuse period at the age of 15 years. After the first period there was an amenorrhea of two months followed by a short period of time in which she flowed two or three times each month. At the age of 16 years the cycles became regular, occurring every twenty-eight to thirty days. The menstrual flow has always lasted seven days. This subject was underweight until the age of 22 years, when, following an appendectomy, her weight became normal.

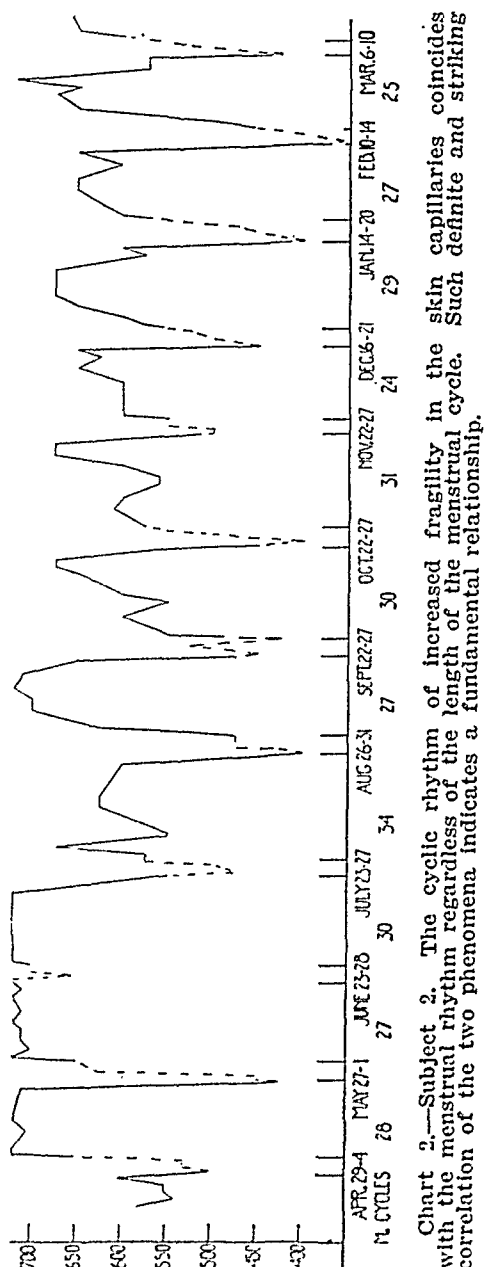


Chart 2.—Subject 2. The cyclic rhythm of increased fragility in the skin capillaries coincides with the menstrual rhythm regardless of the length of the menstrual cycle. Such definite and striking correlation of the two phenomena indicates a fundamental relationship.

This subject was under observation from April, 1937 through March, 1938, during which time 12 menstrual cycles were studied. The cycles were 28, 27, 30, 34, 27, 30, 31, 24, 29, 27, and 25 days in duration (Chart 2). In this subject, as in the previous one, capillary hemorrhage was produced with much greater ease on the first and second days of each menstrual flow. The differences in pressure readings were definite, in one instance being 275 mm. Premenstrual declines in pressure levels were the rule. Greater difficulty in producing capillary hemorrhage in the latter days of the menstrual flow was a constant finding, similar to that noted in the previous subject. The only exception was observed with the flow in September

The charts presented here are representative of the normal group. One chart of a subject with functional bleeding is included merely to demonstrate the variation from the normal. Along the horizontal plane of the charts the days are plotted. Along the vertical plane, the degree of vacuum necessary to produce capillary hemorrhage is indicated in millimeters of mercury. Menstrual bleeding is indicated by broken lines. During the time the subjects were on their yearly vacations, readings were not taken. This is indicated in each instance by interruptions of the graph.

SUBJECT 5.—Subject 5 is a normal individual, 34 years of age. She is 5 feet, 5 inches tall and weighs 125 pounds. Before puberty she was slightly overweight. Her weight became normal, however, at the age of twelve. Menstruation began at 12½ years of age. The cycles have always been of twenty-eight to thirty days' duration. The flow which is moderate lasts six to seven days. On the first day of flow she has cramps that occasionally are severe.

This subject was observed for seven menstrual cycles from April through October, 1937 (Chart 1). The menstrual rhythm is regular. The cycles were respectively of 31, 28, 30, 33, 26, and 34 days' duration.

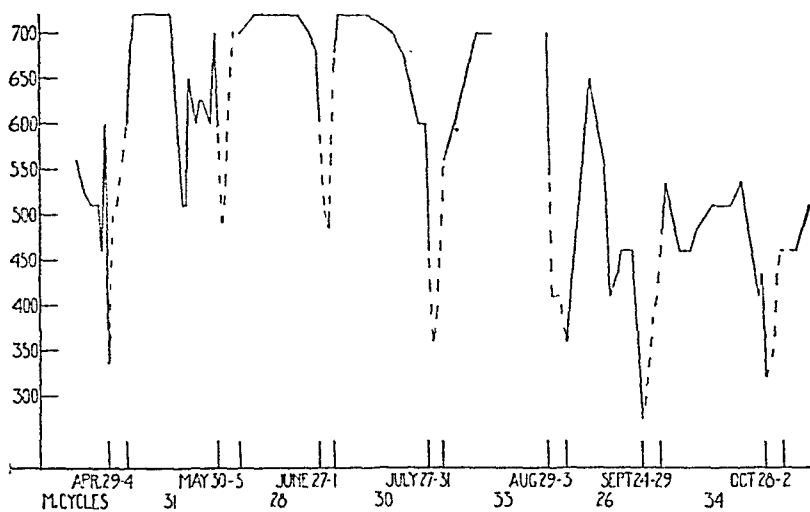


Chart 1.—Subject 5. The negative pressures necessary to produce capillary hemorrhage are indicated in millimeters of mercury on the vertical plane. During the first two days of menstruation an increase in capillary fragility is clearly demonstrated. There is also a moderate premenstrual increase.

In Chart 1 the typical reaction in the skin capillaries is demonstrated. The most frequent reaction noted is shown best in association with the menstrual flow beginning July 27. There is a gradual premenstrual decline in the degree of vacuum required to produce capillary hemorrhage. In this instance it was equivalent to 100 mm. of mercury. On the first and second days of the menstrual flow there is a sudden additional decline, equal here to 250 mm. of mercury. During the remainder of the flow capillary hemorrhage becomes more difficult to produce, so that within one to four days after cessation of menstruation the capillary fragility is at a level commensurable with that of the previous intermenstruum. Minor variations of this pattern or reaction are noted in conjunction with the flow of May 30. Here the entire premenstrual phase is accompanied by increased capillary fragility. Such reactions are described fully with the chart of Subject 18. Chart 1 clearly demonstrates that on the first and second day of every menstrual flow capillary hemorrhage is produced with greater ease than at any other time in the cycle.

During the intermenstruum a minor fall in the required pressure is frequently noted. The significance of this is not immediately apparent. On the whole the intermenstrual pressures necessary to produce capillary hemorrhage are relatively constant. During the months of September and October the general level is lower than that of the preceding months. Similar variations are noted in most of the subjects studied.

SUBJECT 18.—Subject 18, 28 years of age, is 5 feet, 2 inches tall and weighs 104 pounds. She first menstruated at 10½ years. The cycles have always occurred regularly every twenty-six to twenty-nine days. The length of flow is five to six days and is characterized by a sudden onset of brisk bleeding. After three days the flow diminishes gradually. Approximately one week before the onset of flow the breasts become markedly tender, the subject feels tense and becomes nervous and irritable. It is of interest to note that extreme physical work relieves these premenstrual symptoms to a large extent.

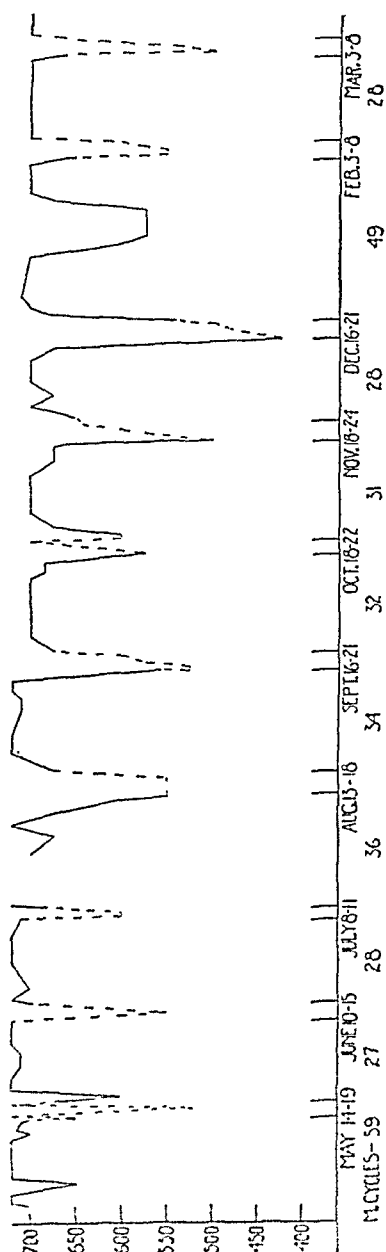


Chart 3.—Subject 10. The correlation of the rhythm in the skin capillaries and in menstruation is definitely shown. The January period was missed but the usual menstrual molimina appeared and disappeared simultaneously with the rhythm of increased and decreased capillary fragility. The prolonged period of increased capillary fragility associated with the menstrual flow of August 13 was accompanied by dysmenorrhea and a profuse flow.

Eleven menstrual cycles were studied in this subject from April, 1937 through February, 1938. The cycles varied from twenty-six to thirty-two days in duration (Chart 4).

During April, May, June, and July capillary hemorrhage was difficult to produce. During this time the reaction in the skin capillaries in association with menstruation was less profound. The subject stated that in these months the menstrual flow was much more scant than her usual normal. The remaining months of the investigation demonstrated a general lower level with wider ranges of variations in capillary fragility.

which clinically was no different from the subject's normal flow. In this instance a secondary increase in capillary fragility occurred late in the period of flow.

The sudden fall in negative pressure invariably occurred in association with the flow regardless of the duration of the cycle. This is demonstrated in the cycles of thirty-four and twenty-four days' durations. The typical pattern of the normal reaction so far described is varied in one cycle in this subject. In June there was no increase in capillary fragility on the first day of flow. As noted on the chart, the fall in negative pressure did not occur until the third day and then was only 70 mm. This very meager reaction in the peripheral vascular system was associated with a very scant menstrual flow from the uterus.

During the intermenstruum in the May, June, and July cycles, capillary hemorrhage was difficult to produce and the level of pressure as shown on the chart was constant. In the months of August, October, November, and December the intermenstrual pressure levels were consistently lower.

SUBJECT 10.—Subject 10, aged 26 years, is 5 feet, 6 inches tall and weighs 117 pounds. Her weight has been normal throughout life. Menstruation began at the age of 15. Since the onset the cycles have been irregular, in that the flow occurred every two to four months. At one time there was five months' amenorrhea. The menstrual flow is moderate in amount and lasts seven days. Since the beginning of the present experiment in April, 1937, the cycles have been more regular and the duration of the flow has decreased to five days. The menstrual flow is moderate in amount the first three days and scant the last two.

During the last two years, two menstrual periods have been accompanied by severe menstrual cramps. With one of these she fainted. One occurred during this experiment. She is emotionally upset, nervous, and irritable before every menstrual period. Activity during this time relieves the symptoms.

The subject was observed from April, 1937 through March, 1938 during which time 10 menstrual cycles were studied. The cycles studied were more normal in regard to regularity of rhythm than the patient had experienced at any previous time. The cycles were, respectively, 59, 27, 28, 36, 34, 32, 31, 28, 49, and 28 days in duration (Chart 3).

In this subject regardless of the lengths of the cycles there was at the onset of menstruation a sudden fall in the negative pressure required to produce capillary hemorrhage. The pattern varied to some extent from that noted in the more normal individuals. Whereas the reaction in the more normal subjects as described above was typified by increase in capillary fragility on the first and sometimes the second days of flow, the increase noted here continued through the third day. This more slow response is consistent with the high and unusually constant level of capillary fragility noted throughout the year in this subject. In two instances (Chart 3, June 10 and July 8), there was no increase in the capillary fragility until after the first day of menstruation. This is an unusual finding. During the remainder of the flow the pattern duplicated the normal.

The menstrual flow of Aug. 13, 1937 was accompanied by a type of reaction in the skin capillaries that differed from the usual reaction observed in this subject. One week prior to the onset of flow a rapid decline in negative pressure occurred. This low level persisted through the first four days of menstruation without any additional drop during menstruation. Thus, the negative pressure remained at a constant low level for six days, unlike the findings in the other cycles of this subject. Associated with this varied pattern, the subject had a very profuse flow and a very severe dysmenorrhea. The significance of this is dealt with in the discussion.

Chart 3 shows that menstruation did not occur in January, 1938. Near the expected time of menstruation in January, the subject had all of the usual symptoms that precede menstruation. She stated she anticipated the flow within a day or two. Associated with these clinical symptoms of impending menstruation, there was a definite increase in capillary fragility. After several days, during which time the lower pressure level was maintained, the subject reported that the clinical symptoms were disappearing and that she did not think she would menstruate. In exact correlation with these altered symptoms the capillary fragility decreased and returned to a normal intermenstrual state without the occurrence of menstruation.

Exactly corresponding to the time in the premenstruum when skin capillary hemorrhages were produced with relatively great ease, this subject noted subjective symptoms of impending menstruation. The most intense symptoms were evident just before the menstruations of November 27 and February 25. These two periods were preceded by the most profound and prolonged increase in capillary fragility.

SUBJECT 30.—Subject 30, aged 27 years, weighs 107 pounds and is 5 feet, 6.5 inches tall. Before puberty she was underweight, but since then she has weighed as

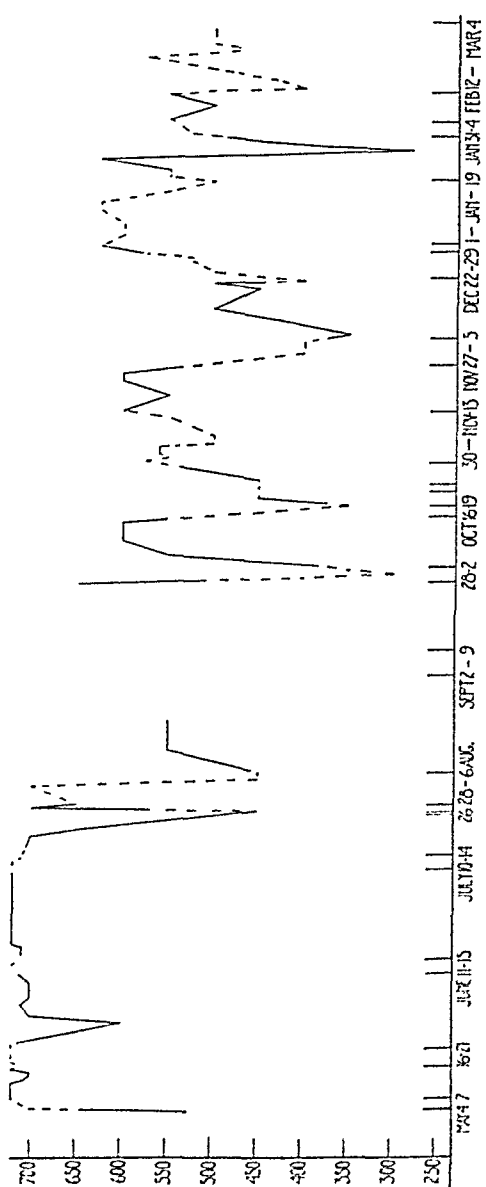


Chart 5.—Subject 30. There is no demonstrable cyclic rhythm in capillary fragility. The menstrual rhythm is entirely irregular. There is no correlation between the two phenomena in this subject with functional uterine bleeding.

much as 140 pounds. Menses began at 13½ years. The flow was regular every twenty-eight days and lasted four days until the age of 23. Since then she has been entirely irregular, having metrorrhagia and menorrhagia. With the abnormal bleeding, dysmenorrhea has been severe. Examination revealed normal pelvic organs.

This subject was observed from May, 1937 to March, 1938. The cycles were entirely irregular (Chart 5), in that the subject flowed both too often and too long. The menstrual flow of May 4, 1937 was accompanied by a decrease in the fragility of the skin capillaries, unlike that observed in normal menstruation. The uterine bleeding of May 16, June 11, and July 10 occurred without any variation in the

Typical findings at menstruation are exemplified during the flow of Oct. 3, 1937. The late premenstrual phase is accompanied by increased capillary fragility, and on the first day of flow a marked increase in fragility is noted. In the November, January, and February cycles a slight modification of this reaction occurred. The alteration in capillary fragility in the premenstruum took place several days before menstruation began and the increase in fragility was marked. In one instance it

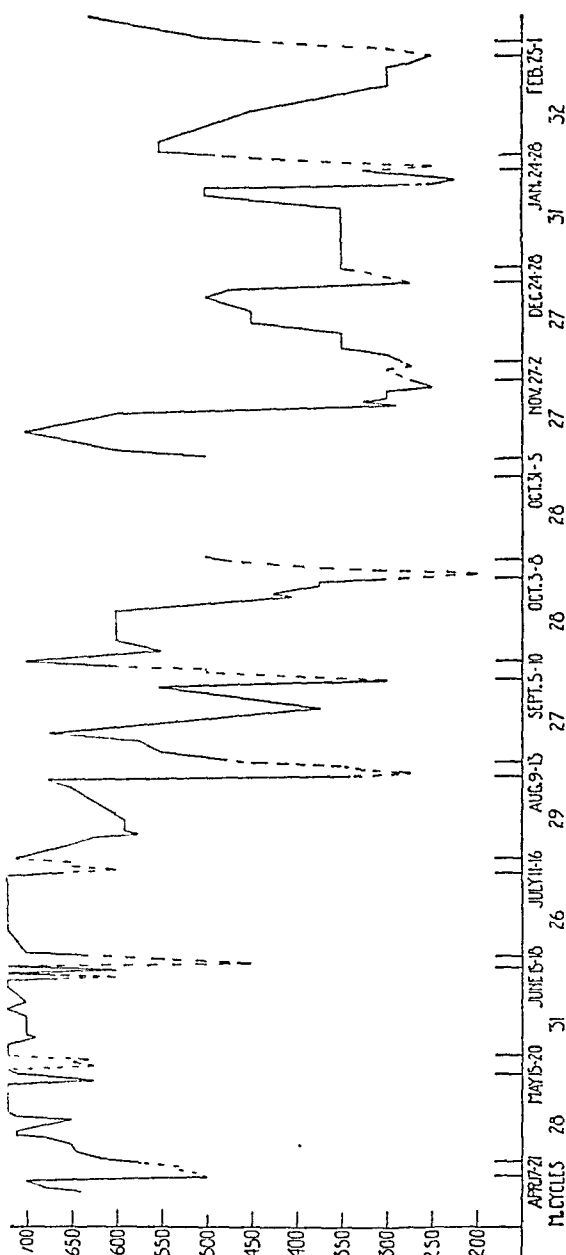


Chart 4.—Subject 18. The rapid premenstrual changes in capillary fragility are associated with the appearance of menstrual moulins and in two instances with slight uterine bleeding. Menstruation since August has been profuse. During the four previous months the flow was scant.

was equivalent to 300 mm. of mercury in twenty-four hours. In the three cycles mentioned the low premenstrual levels were maintained without any further significant changes in capillary fragility on the first day of flow.

With the marked increase in the ease with which capillary hemorrhage was produced a few days before the onset of menstruation on January 24, there was a slight uterine bleeding characterized as spotting. Likewise, just prior to menstruation on June 15, there was a premenstrual increase in capillary fragility associated with simultaneous uterine bleeding for three hours.

occur together (Charts 2 and 3). Additional evidence is obtained from the demonstration that the sudden premenstrual increase in capillary fragility several days before the onset of menstruation is occasionally accompanied by slight uterine bleeding (Chart 4, June 15 and January 24).

Of importance in this respect is the direct correlation of the so-called menstrual molimina with the premenstrual phase of increased capillary fragility (Chart 4). Absolute proof that these two are directly associated is obtained in Subject 10. In this subject menstruation which was expected in January, 1937, failed to appear, but the skin capillaries evidenced the usual cyclic phenomenon that coincided with menstrual rhythm. In complete accord with the increase and then the decrease in capillary fragility at this time, menstrual molimina appeared and disappeared. Gebert (1936) reported the appearance of menstrual molimina in two instances of altered dermatographic latency time in the premenstruum.

In the intermenstruum, the negative pressures required to produce capillary hemorrhage may be relatively constant as noted in Subjects 5 and 10. On the other hand there are numerous instances in which there is a brief period of increased capillary fragility near the midpoint of the cycle.

In some subjects (Chart 4), the intermenstrual levels varied considerably during the course of the experiment. The general trend of the entire group is toward an increased fragility of the capillaries during the fall and winter months.

In Subject 10 the apparent high resistance of the capillary endothelium as indicated by the high pressures required to produce capillary hemorrhage, the lack of variations during the year of study, the delayed response on the first day of menstruation, and the continued but slight increase in capillary fragility extending through the third day of menstruation which is unduly long, suggest the fact that in this individual a corresponding resistance of the capillaries in the uterus or possibly their inability to adequately respond might explain the coexistence of amenorrhea.

Conclusive evidence that the phenomenon described is an integral part of normal menstruation is the demonstration that in association with abnormal or functional uterine bleeding this reaction is completely dissociated (Chart 5). Endometrial biopsies were studied as a guide to the character of the bleeding. In a later paper this phase will be fully elaborated upon.

That capillary hemorrhage is produced experimentally with greater ease at the time of menstruation has been reported by Stephan (1921). In studying various diseases by means of the Rumpel-Leede phenomenon, he observed that the phenomenon was likely to be positive in women during menstruation. Seyderhelm and Heinemann (1930) described similar findings. Pistor (1935) stated that petechial hemorrhages could be produced during the actual flow but rarely during the first half of the cycle.

peripheral vascular phenomenon. On July 26, uterine bleeding was present for this one day only and was associated with an increase in capillary fragility. Two days later, however, menstruation took place irrespective of the state of capillary fragility of the skin capillaries. The pattern of reaction in the skin capillaries with the onset of menstrual flow on September 28 duplicates that seen in the normal subjects. In the group of functional bleeders, normal reactions interspersed among reactions at variance with the normal are observed frequently.

Through the remainder of the chart it is evident that there is no correlation between the skin capillary reaction and uterine bleeding. Endometrial biopsies taken at intervals reveal an endometrium without the influence of a corpus luteum.

SUMMARY AND DISCUSSION

In association with menstruation in the normal subjects studied, a fairly uniform series of events occurs in the skin capillaries. These events are variations in capillary fragility, or capillary resistance, or, as I prefer to designate it, the phenomenon of capillary hemorrhage.

In normal subjects on the first day of the menstrual flow, there is uniformly a considerable increase in ease of producing capillary hemorrhage. The changes in the required negative pressures occur with marked rapidity. Measured in millimeters of mercury indicative of the degree of vacuum required to produce the capillary hemorrhage, this marked and rapid change varies from 75 to 300 mm. In some instances the variation may be as great as 200 mm. of mercury within two hours. There is frequently a small additional increase in capillary fragility on the second day of flow. During the remainder of the menstrual flow the capillaries become more resistant. In other words, capillary hemorrhage becomes increasingly difficult to produce during the remainder of the menstrual flow. By the second or third day after the cessation of the menstrual flow, the negative pressures required to produce capillary hemorrhage reach a level approximately the same as that observed during the previous intermenstruum. As demonstrated in the charts, this pattern of reaction in the peripheral vascular system takes place at the approximate time of menstruation regardless of variations in the lengths of the menstrual cycles or menstrual flow.

During the late premenstrual stage there is usually a gradual increase in capillary fragility (Chart 1, July 27). In some instances the increase is relatively slight while in others it is great (Chart 4, November 27). As a rule the premenstrual change is followed by rapid increase in capillary fragility upon the first day of flow as noted above (Chart 1, July 27). Those instances which evidence continued low premenstrual readings are usually not followed by significant changes with the onset of menstruation (Chart 4, November 27).

Another modification of the demonstrable reaction in the premenstrual stage is concerned with a decreased capillary fragility one to three days prior to menstruation (Chart 4, August 9 and Chart 1, May 30). These variabilities in the type of reaction are not inconsistent with such a biologic phenomenon as menstruation.

Indicative of the fact that these skin capillary phenomena are associated with menstruation is the consistent regularity with which the two

results. The pattern of reaction reduplicates that observed in the peripheral vascular system in normal women during the bleeding phase of the cycle (Chart 2, May 27).

2. The vasospasm produced by the adrenalin injections was associated with subjective clinical symptoms identical to those observed by the patients immediately before menstruation. In correlation with this is the fact that in many of the subjects (Subjects 10 and 18; Charts 3 and 4) subjective symptoms of impending menstruation developed simultaneously with the increase in capillary fragility, which I believe is the result of vasospasm.

3. Vasospasm of the skin vessels was observed directly by Hagen (1922). By the use of a capillary microscope he noted spasm in these vessels during the premenstrual period. During the time of active flow the spasm relaxed.

4. Eichbaum (1929) observed that epinephrine produced less increase in blood pressure during menstruation than at other times of the cycle and concluded this was due to the fact that the smooth muscle was already in spasm at this time.

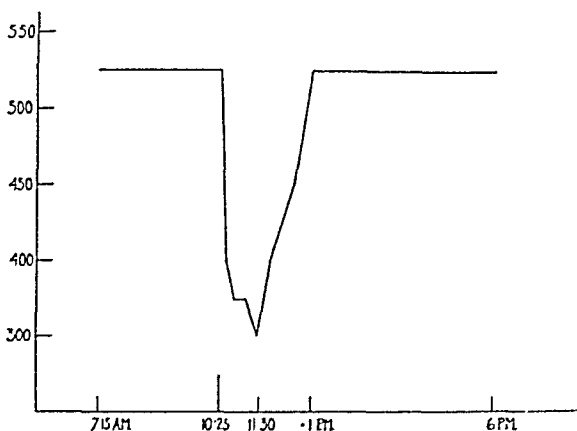


Chart 6.—This demonstrates increased capillary fragility following the subcutaneous injection of 0.2 c.c. of 1:1000 adrenalin solution. The increase in capillary fragility occurs at the time that spasm in the skin vessels is evidenced by blanching of the skin. The initial sudden increase came ten minutes after injection. The entire reaction duplicates that observed in the skin capillaries in association with menstruation.

5. Gebert (1936) noted a delay in the time of the dermographic reaction to skin irritation in the premenstrual phase of the cycle and ascribed it to the fact that the skin capillaries were in spasm. Petersen (1934) has described vascular spasm and states that the peripheral vasospasm occurs in association with the menstrual rhythm irrespective of meteorologic conditions.

6. DeLisi (1935) demonstrated by chemical tests that there was a premenstrual increase in the epinephrine content in the blood with an associated rise in blood pressure which is consistent with the occurrence of vascular spasm.

7. The changes noted in capillary fragility in this work and the altered capillary fragility and permeability noted by others can and do result from vascular spasm (Landis, 1937, Petersen, 1936, and others). Landis (1937) states that vascular spasm produces an anoxemia of the capillary endothelium. This reaction of spasm and anoxemia, he concludes, is reversible unless the anoxemia goes too far, in which case the

Clinically, the increased frequency of hemorrhage at the menstrual period is recognized. There is also the well-known phenomenon of vicarious menstruation.

Kieser (1933) among many others, described hemorrhages from the nose, rectum, lung, and urinary bladder accompanying or replacing the uterine bleeding. Saitz (1935) observed small hematomas in the urinary bladder near the trigone on the first day of menstrual flow. Pottenger (1925) stated that hemorrhage from tuberculous foci was accompanied by an increased capillary permeability and hemorrhage.

Minot (1936) recorded three cases of intermittent menstrual purpura hemorrhagica with lymphocytosis and a decrease in the platelet count. David's cases (1926) of hemorrhagic diathesis at menstruation differed in that the platelets were not reduced. Ellman and Weber (1935) also described recurrent menstrual purpura. Other similar instances too numerous to mention have been recorded.

It is necessary also to mention menstrual edema. Thomas (1933) observed 2 patients who had edema only at the menstrual period. Molnár and Gruber (1934) described an edema of unknown origin occurring at the time of menstruation. Sweeney (1934) recorded the gain in weight and edema at menstrual time in a group of menstruating women. Atkinson and Ivy (1936) described a case of menstrual edema in which the edema appeared one week prior to the onset of menstruation. They also mention two other patients with premenstrual edema.

These phenomena of hemorrhage and edema that occur in the body in association with menstruation have been ascribed to various factors.

Seyderhelm and Heinemann (1930) believed the hemorrhages were the result of a lowering of the endothelial resistance which was determined by a lowering of the estrogen content of the blood. David (1926) concluded the changes were the result of ovarian dysfunction. Pistor (1935) stated that the endothelial system was influenced by ovarian hormones by way of alteration in the blood cholesterol. Pottenger (1925) held that a menstrual enzyme was responsible.

That the changes are incident to vascular spasm is suggested by many facts. 1. Similar changes in the skin capillaries as those observed during menstruation (increased capillary fragility) can be brought about by the production of vascular spasm in the skin vessels. This was demonstrated as follows. Eight human subjects were chosen, one female and seven males, and into each adrenalin was injected. Males were used in order that the menstrual rhythm would not interfere. Tests were made before injection to establish the normal negative pressures required to produce capillary hemorrhage for each individual.

To each individual then, 0.1 c.c. to 0.4 c.c. of 1:1000 adrenalin solution was injected subcutaneously following the method of injection suggested by Luckhart and Koppányi (1926). These amounts of adrenalin produced in all the subjects a generalized blanching of the skin and a marked ischemia about the site of injection. Each promptly developed a tremor, nervousness, palpitation, and increased pulse rate.

In all the individuals so treated there was within twenty to forty-five minutes, while the general blanching was still evident, a definite, abrupt decrease in the negative pressure required to produce capillary hemorrhage (Chart 6). This decrease amounted to between 100 and 200 mm. of mercury. A return to normal occurred usually within two hours. The experiment was repeated three different times with identical

August 13) an unusually prolonged period of vascular spasm in the skin capillaries was accompanied by severe dysmenorrhea and profuse menstruation, probably dependent upon coexisting spasms in the vessels in the uterus.

CONCLUSIONS

1. This study indicates that in the human female with normal ovulatory menstruation, there are rhythmic changes in the capillaries of the skin that are associated with the cyclic menstrual rhythm.

2. These rhythmic changes are essentially changes in capillary fragility.

3. During the few days prior to and on the first day of menstruation, capillary hemorrhage is produced with relatively greater ease than during the remainder of the cycle.

4. It is indicated that these rhythmic changes are the direct result of vascular spasm.

5. In functional uterine bleeding, the vascular rhythm in the skin capillaries is profoundly disturbed, and it is completely dissociated from the menstrual rhythm.

6. These facts indicate that menstruation which is evidenced as a local vascular phenomenon is in reality a part of a demonstrable generalized vascular phenomenon present in the entire body.

I would like to express my appreciation for technical assistance rendered by Barbara Phares.

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reaction then produces a nonreversible increase in permeability. It is conceivable that rupture of the capillaries with consequent hemorrhage might occur with relatively more ease upon resumption of circulation. Bartelmez (1933) has demonstrated this microscopically in the uterine endometrium at the onset of menstruation. Such phenomena of vasospasm with altered permeability at menstrual time might well explain the occurrence of menstrual edema.

8. Vasospasm occurs in the uterus simultaneously with the increase of capillary fragility demonstrated in the capillaries of the skin. In the uterus, particularly in the endometrium, a vascular rhythm has been demonstrated. It consists of rhythmic spasms of the terminal arteries and arterioles which coincide with the rhythmic changes observed in this paper in the peripheral vascular field.

Lahm (1926) described one uterus in which he noted vasoconstriction in the spiral arteries in the myometrium and deeper portions of the endometrium. Meyer-Rüegg (1918-1919) noted a similar phenomenon. To Bartelmez (1933), Markee (1933), and Daron (1936) belongs the credit for conclusive establishment of the facts and the complete description of the details of vascular spasm in relation to menstruation. The spasms, as observed by Markee in *Macacus rhesus*, became evident about the nineteenth day of an ovulatory cycle. As the time of menstruation approached, the spasms occurred more frequently and each lasted for a longer time. Just before the onset of the flow some individual spasms persisted for twenty-four to forty-eight hours. Bartelmez (1933) has concluded that in the human being the spasms produced an ischemic necrosis of the capillary endothelium and the superficial endometrial tissues. Upon relaxation of the spasm the resumed circulation burst the capillary walls and a superficial subepithelial hematoma was formed. Markee (1933) observed this in ocular transplants. Subsequent desquamation of the superficial endometrial tissue occurred in the region of the particular vessel that evidenced prolonged spasm. Thus, these workers concluded that physiologic vasoconstriction was adequate to account for the tissue loss and the bleeding that characterizes any type of menstruation.

Extensive and profound vascular spasm in the uterus was described by Bartelmez (1933) and Markee (1933) to vary in its time of onset. The phenomenon occurred at times in its most profound state a day or two before menstruation and at other times only an hour or two before. Similar variations in the time of appearance of the marked increase in the fragility of the skin capillaries in the subjects of this experiment (Chart 2, May 27 and Chart 4, November 27) suggest a close relationship of the two phenomena.

9. Finally, the demonstrated generalized vasospasm with resulting anoxemia and ischemia may readily account for the various phenomena associated with menstruation. These phenomena occur only at menstruation, and it is only at this time that vascular spasm is evident. Some of these are: epileptic seizures only at menstruation, vicarious menstruation, hemorrhages in various tissues and organs at menstruation and late premenstrual stage, diarrhea occurring regularly at menstrual time, and menstrual edema. In some cases of hemorrhagic diathesis hemorrhage occurs at menstrual time in spite of the fact that no variations in the characteristic blood picture can be shown. The added factor of a generalized vasospasm and increased capillary permeability at menstruation, demonstrated in this paper, might well explain such a phenomenon.

Tangible evidence is offered in support of the suggestion that ischemia in the uterus may be a cause of dysmenorrhea. In Subject 10 (Chart 3,

body temperature and basal metabolism accompanying the menstrual cycle. Since there are so many general phenomena involved, it seems unwise to conclude without further evidence, that the particular change which the author has studied is the one responsible for the initiation of menstruation in the uterus.

It may be of interest to mention that Dr. Chassar Moir of London has postulated vascular spasm in the uterus as an explanation for the painful contractions of dysmenorrhea. This was based upon the fact that the arterial pulsations transmitted from a recording balloon inserted in the uterus, disappeared at the height of the uterine contractions. Drs. Lackner, Krohn, and myself had occasion to make similar observations in our studies on uterine motility in dysmenorrhea. We used a more sensitive recording system and found that even at the height of the severe uterine contractions of dysmenorrhea, the arterial pulsations persisted. This observation speaks against vascular spasm in the uterus, even under conditions where such spasm might be expected to be greater than normal.

My remarks are not intended to show that Dr. Brewer's interpretation of his results is wrong, but I think they do indicate that his conclusions are somewhat premature.

DR. BREWER (closing).—I, of course, knew there were many other phenomena associated with menstruation, but the paper was concerned only with the changes in the peripheral vascular system.

UNPREDICTABILITY OF THE PHENOMENA ACCOMPANYING THE MENSTRUAL CYCLE IN NORMAL WOMEN*

WITH SPECIAL REFERENCE TO THE TIME OF OVULATION

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SCIENTIFIC interest in the determination of the exact time of ovulation in the menstrual cycle has been somewhat overshadowed by the less critical, popular interest in the related Ogino-Knaus theory of the so-called "safe period." It may be accepted that the period of fertility during a menstrual cycle is restricted to a certain number of days preceding and following ovulation, depending upon the duration of viability of the sperm and the unfertilized ovum. The establishment of a "safe period" for a particular woman therefore depends upon the accuracy with which we can determine or predict the time of ovulation for her, and also upon the correctness of our assumptions as to the life-span of the free sperm and ova.

The time of ovulation in women has been approximated by a number of investigators in a variety of ways.¹⁻¹² But the most widely exploited method in normal women probably has been that of Knaus^{1,2} based upon observations of the motility of the uterus and the reaction of this organ to the administration of extracts of the posterior lobe of the pituitary gland. According to Knaus, the uterus of the nor-

*Presented at a meeting of the Chicago Gynecological Society, March 18, 1935.

DISCUSSION

DR. CARL A. JOHNSON.—The importance of circulating substances as regulatory factors of the blood vessels has recently been brought forcibly to our attention. A few years ago there was great enthusiasm for the surgical relief of vasospastic conditions of the extremities through operations on the sympathetic nervous system. Reports of success were, however, short lived because of the recurrence of symptoms. The circulation apparently returned to the preoperative condition within a comparatively short time following these operations. Studies soon showed that sympathectomized blood vessels became sensitive to circulating substances in the blood, particularly epinephrine.

These investigations and those of Dr. Brewer stress the importance of the hormonal control of the blood vessels, not only with regard to vasoconstriction and vasodilatation, but also to hemorrhagic conditions. This study should mark only the beginning of investigations of the effects of other hormones upon the peripheral blood vessels.

DR. GEORGE BARTELMEZ.—This additional evidence (Dr. Brewer) that the phenomenon of menstruation involves general bodily changes is significant. The conclusion is that we are dealing with general changes in the body as a whole. The uterine vessels, however, are more sensitive than any others and they alone suffer extravasation, normally.

One of the most important of Dr. Brewer's findings is the demonstration of a fundamental difference between menstruation and functional bleeding. That this method may be used to differentiate between ovulatory and nonovulatory cycles is unlikely, because we have now enough evidence to state that there are transitions between the typical ovulatory cycle and cycles in which ovulation has not occurred. Such intermediate conditions may be associated with cystic follicles or with early regression of the corpus luteum.

DR. WALTER SCHILLER.—When physiologists began to investigate the cyclic functions of female genitalia, they placed menstruation in the foreground, considering it as the summit of the cyclic changes. In time this conception was changed, when it was realized that the purpose of the intermenstrual changes is not menstruation but pregnancy. The changes the female organism undergoes to adapt itself for gestation, start immediately after ovulation. Menstruation only signifies failure in establishing gestation and the cancellation of the preparations for this gestation. Founded on this interpretation, we have changed the term premenstrual changes, to the term pro gravid changes, expecting to find the maximum of pro gravid changes in the premenstrual phase.

In agreement with this, a great number of determinations carried out by physiologists proved that the maximum of changes concerning blood morphology, blood biochemistry, blood pressure, etc., can be found not during menstruation, but during the premenstrual phase. Keitler, by careful investigation of 60 cases of so-called vicarious menstruation, proved that the extrauterine bleeding takes place in the phase of premenstrual hyperemia, and in consequence of loss of blood the uterine bleeding is reduced.

Joseph Novak, of Vienna, confirmed that laparotomies in which the abdominal wall is hyperemic generally are carried out in the premenstrual phase, whereas the so-called "dry" laparotomies, in which there is very little hemorrhage during section of the abdominal walls, are performed in the postmenstrual phase. The most interesting findings of Dr. Brewer's work correspond to these findings and confirm the fact that the maximum of physiologic changes are found during the premenstrual phase.

DR. SAMUEL SOSKIN.—The previous discussers have already emphasized the fact that menstruation is not a process confined to the uterus, but is accompanied by general changes throughout the body. In this connection one might also mention the recent work of Rubenstein who has demonstrated rhythmic changes in the

arations, to observe the state of the uterine endometrium, and to determine the urinary excretion of prolan and estrin, as frequently as possible during the menstrual cycle of normal women. The particular difficulty of this work was to induce normal women to undergo repeatedly the necessary inconveniences and minor discomforts involved. There was also the important consideration that too frequent disturbance of the uterus, especially as regards endometrial biopsy, might interfere with the normality of our conditions. The procedure finally adopted represents a compromise between the theoretically desirable and the practically expedient.

We were able to make the above observations, once in each quarter of the menstrual cycle, in each of 15 normal women. However, the 4 sets of observations on each woman were not made during a single cycle. In most of the cases they extended over 2 cycles, the studies being made during the first and third quarters of one cycle, and during the second and fourth quarters of the next. In some cases, each of the 4 sets of observations was made during a quarter of 4 different cycles. For purposes of comparison, careful records were kept of the exact length of every cycle during which the subjects were studied.

Our experimental methods have been fully described in a previous publication.¹⁷ On the day of the experiment, a rubber balloon was inserted into the uterus with aseptic precautions. After a half hour rest period, to allow for recovery from the initial disturbance, if any, the kymograph record of uterine motility transmitted from the balloon was begun. Fifteen minutes later, 1 c.c. of obstetric pituitrin (Parke-Davis) was injected intramuscularly. A second injection of pituitrin, or an injection of pitocin or pitressin, was administered fifteen minutes after the first injection. The kymographic tracing was continued for at least half an hour after the last injection. A strip of uterine mucosa was removed by suction curette after each experiment. Eight of our subjects made twenty-four-hour urine collections on the days preceding their experimental days and ending on the morning of the latter. These specimens were assayed for prolan and estrin content.

RESULTS

There would be little purpose in attempting to give all our results in detail here, because their rather considerable bulk renders them unwieldy and difficult to correlate. We have chosen, instead, to present brief summaries of those data which seem to yield significant correlations. Some examples and trends are graphically illustrated.

UTERINE MOTILITY, AND RESPONSE TO PITUITRIN

A total of 60 kymograph tracings of uterine motility was made in our 15 normal subjects; 30 records during the first half of the menstrual cycle, and 30 during the second half. Of the 30 tracings made during the first half of the cycle, only 8 showed definite spontaneous uterine motility. There was no instance of spontaneous motility in the second half of the cycle, except for 3 tracings made within forty-eight hours of the onset of the next menstrual period. Thus while the trend of these results follows the pattern described by Knaus, the large number of quiescent uteri during the first half of the cycle makes it impossible to use the presence or absence of spontaneous uterine motility as a criterion of time in the menstrual cycle. Incidentally, however, the fact that 49 out of the total number of 60 records showed no uterine contractions after insertion of the balloon, answers Dickinson's (discussion¹⁴) criticism of the balloon method. It does not seem likely when uterine contractions are found that they are merely the result of the presence of a foreign body in the uterus.

The intramuscular injection of 1 c.c. of pituitrin caused increased uterine motility in only 23 of the 30 trials during the first half of the cycle, and in 8 of these cases the reaction was very slight. Of the 22 tests made before the last two days of the second half of the cycle, all of which should have been negative according to Knaus, only 12 were negative while 10 showed a definite response to pituitrin. The 8 tests

mal woman manifests spontaneous, rhythmic contractions during the first fourteen days of a twenty-eight to thirty-day menstrual cycle. During this portion of the cycle, which may be termed the follicular phase, the uterus responds with increased contractions to the administration of posterior pituitary extract. Ovulation occurs on the fifteenth day. Twenty-four hours later the uterus has become flaccid and quiescent, and no longer responds to posterior pituitary extract. This corpus luteum phase lasts from the sixteenth day of the cycle until forty-eight hours before the ensuing menstruation. At this time the uterus reverts to the motility and responsiveness characteristic of the first fourteen days of the cycle. If one can accept these findings of Knaus as correct, then one can believe with him that it is possible to determine the date of ovulation with some degree of exactitude, by observing the day of the cycle upon which the uterus ceases to respond to the administration of pituitrin. It would thus be possible to establish the "safe period" for healthy women with regular menstrual periods, providing the duration of viability of the sperm and ovum were known.

Unfortunately, a number of authors have been unable to confirm Knaus's results or to concur in his assumptions.

Klaften and Ruffel¹² found that in 11 cases out of 34 studied by Knaus's technique, their results were opposed to his. Similarly, Tachezy³ studied 20 patients, and found that only 20 out of 67 observations which he made conformed with those of Knaus. Schultze,¹¹ who used a somewhat different technique, has even gone so far as to conclude that the uterine reaction to posterior pituitary preparations is augmented in the second half of the menstrual cycle. Finally, Hermstein⁶ has emphasized the great possibilities of error in calculation of the "safe period," when one considers the uncertainty of our knowledge concerning the viability of the ovum and sperm under different conditions in different parts of the female genital tract. He also points out the variability in the length of the menstrual cycle in many perfectly healthy women at different times. A more complete account of these theoretical considerations will be found in recent review articles.¹³⁻¹⁶

Our interest in the above problem was aroused during our previous studies on the motility of the human uterus.^{17, 18} We had noted considerable variability in the motility, endometrium, blood and urine hormone content, and length of the menstrual cycle, in a few normal women used as controls for other patients. It seemed apparent that, if these normal women were at all representative, the component phenomena of the menstrual cycle were too irregular and unpredictable to form a basis for such calculations as those of Knaus. It therefore seemed worthwhile to study a larger series of normal women by the same methods, and also to observe the effects of the administration of posterior pituitary extract at various times in the menstrual cycle.

METHODS

This work was done on women between the ages of 19 and 42 years, in whom a careful history and a thorough gynecologic examination revealed no abnormality in sexual structure or function. Our object was to record the spontaneous uterine motility and the uterine response to the administration of posterior pituitary prep-

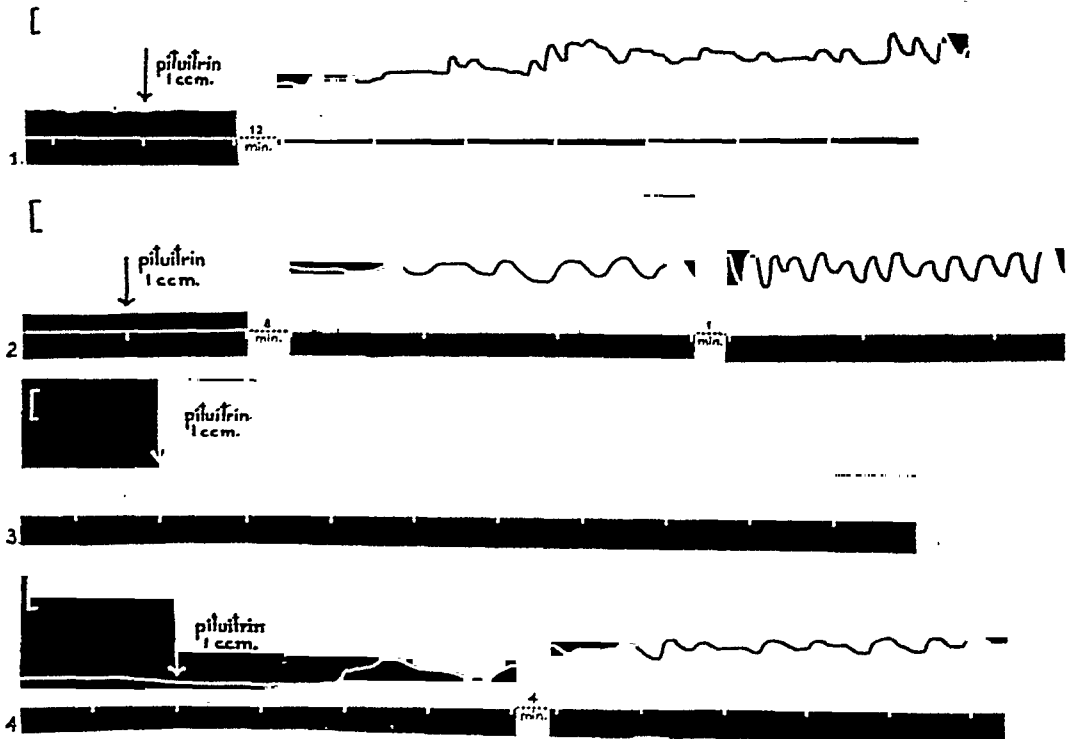


Fig. 2.—Mrs. L. K., aged 29 years. A "Knaus-positive" case.

Record 1: 8th day of a 20-day cycle

Record 2: 10th day of a 22-day cycle

Record 3: 15th day of a 22-day cycle

Record 4: 20th day of a 21-day cycle

Conventions as for Fig. 1.

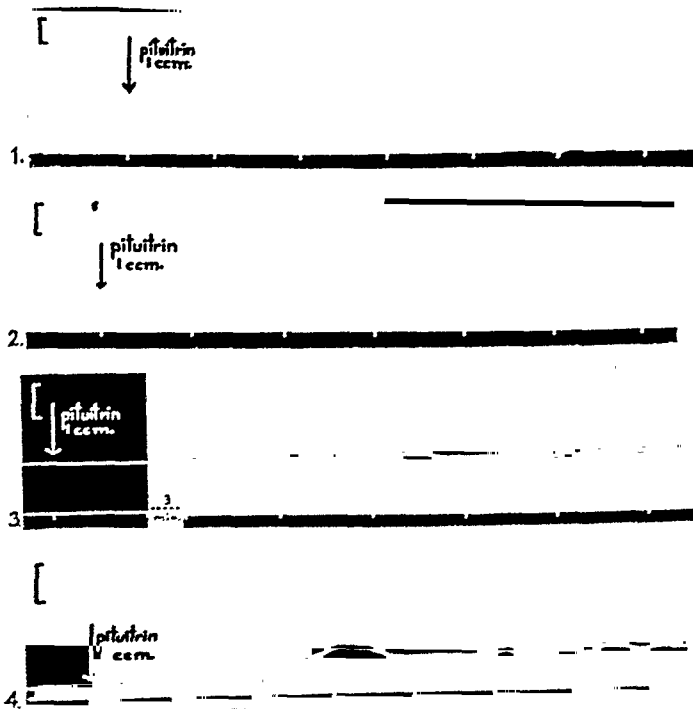


Fig. 3.—Mrs. A. K., aged 39 years. A "Knaus-negative" case.

Record 1: 2nd day of a 29-day cycle

Record 2: 5th day of a 30-day cycle

Record 3: 15th day of a 30-day cycle

Record 4: 22nd day of a 30-day cycle

Conventions as for Fig. 1.

made within forty-eight hours of the next menstrual period, all of which should have been positive according to Knaus, yielded only 5 positive responses while 3 showed no response to pituitrin. The failure in response of any of the above cases can hardly be ascribed to an inadequate dosage of pituitrin, since in no case was a response elicited by the second injection of pituitrin if it had failed to appear after the first dose.

It is apparent, from the above, that the Knaus method of determining the time of ovulation from the uterine response to posterior pituitary extract, is unreliable to say the least. The results of such tests in different, apparently normal women, are unpredictable. Illustrative examples are given in Figs. 1 to 4. Two cases which yielded results like those of Knaus are shown in Figs. 1 and 2. Fig. 3 is from an equally normal woman, who gave completely opposite results. Fig. 4 is a composite of results from 5 different women, showing that the normal uterus may exhibit an increased motility after the injection of pituitrin, in any part of the menstrual cycle. It is noteworthy, however, that the 3 women who yielded the previously



Fig. 1.—Mrs. B. H., aged 42 years. A “Knaus-positive” case. Showing representative portions of records taken at 4 different times during the menstrual cycle.

Record 1: 3rd day of a 24-day cycle
Record 2: 6th day of a 25-day cycle
Record 3: 19th day of a 24-day cycle
Record 4: 21st day of a 24-day cycle

The vertical ticks on the base line represent time intervals of one minute. The calibration mark in the upper left hand corner of each record indicates the movement of the recording lever, equivalent to a uterine contraction which would decrease the intrauterine volume by 1 c.c. The gap in the second record represents a 4-minute period excised from the record, in order to allow more complete presentation of the more significant portion which follows. The straight-line tracing shown in Record 3, means that no uterine contractions whatever were observed throughout the whole of that experimental observation, lasting at least one hour.

cited 11 instances of spontaneous uterine motility before the administration of pituitrin, all fell into the “Knaus-positive” group. It may well be that Knaus’s findings might be confirmed in a selected group of women with particularly active and responsive uteri. But, his results are not obtained in most, apparently normal, women.

UTERINE RESPONSE TO PITOCIN AND PITRESSIN

Some results obtained from a comparison of the effectiveness of pitocin and pitressin (Parke-Davis) with that of pituitrin, in causing increased motility of the

TABLE I. RELATIVE EFFECTIVENESS OF PITUITRIN, PITOCIN AND PITRESSIN IN CAUSING INCREASED UTERINE MOTILITY AT DIFFERENT STAGES OF THE MENSTRUAL CYCLE*

	FIRST HALF OF THE CYCLE	SECOND HALF OF THE CYCLE	LAST 2 DAYS OF THE CYCLE
Pituitrin	$\frac{23}{30}$ 77%	$\frac{10}{22}$ 45%	$\frac{5}{8}$ 62%
Pitocin	$\frac{7}{16}$ 44%	$\frac{2}{14}$ 14%	$\frac{3}{7}$ 43%
Pitressin	$\frac{3}{5}$ 60%	$\frac{0}{5}$ 0%	—
Results according to Knaus	100%	0	100%

*The fractions in the upper left hand corner of the compartments in this table give the actual figures from which the percentages were calculated. The numerator represents the number of instances in which the administration of a particular posterior pituitary preparation was followed by increased uterine motility. The denominator represents the total number of tests made with that preparation, under the specified conditions.

UTERINE ENDOMETRIUM

Fig. 5 graphically presents the results of the histologic examination of 60 endometrial biopsies, taken once in each quarter of the menstrual cycle, in each of our 15 normal women. Because of the varying length of the cycle in different women, and at different times in the same woman, the proportionate rather than the absolute time in the cycle has been plotted. This makes our data comparable as to time, and enables one to judge the tendency of the results in the group as a whole, from the distribution of all the plotted values. The 4 observations on each subject are identically numbered, so that the course of events in each may be followed through the cycle. It may be seen that the group of women as a whole shows the development of endometrial change through the cycle, in the generally accepted manner. But there are enough individual deviations from the general pattern to make the latter an unreliable criterion of normality in any given woman. It is evident at a glance, for example, that 4 out of the 15 normal women (or over 25 per cent) failed to show a secretory endometrium during the last quarter of the menstrual cycle.

It might be supposed that those cases which failed to show a secretory endometrium during the second half of the menstrual cycle, were the same individuals who did not respond to pituitrin in the manner described by Knaus. If this were so, both these phenomena could be ascribed to the occurrence of anovulatory cycles in these women. Correlation of these data, however, reveals the fact that the 10 instances of positive motility response to pituitrin in the second half of the cycle (excluding the last forty-eight hours) occurred in conjunction with 1 negative, 4 proliferative, and 5 secretory specimens of endometrium. The 12 instances in which there was no response to pituitrin, on the other hand, were accompanied by 6 proliferative and 6 secretory specimens of endometrium. This equal division of the incidence of both the secretory and the nonsecretory endometrium between the "Knaus-positive" and "Knaus-negative" cases, forces the conclusion that our results cannot be explained by the supposed occurrence of anovulatory cycles.

URINARY EXCRETION OF PROLAN AND ESTRIN

The twenty-four-hour urinary excretions of prolan and estrin, in 8 of our subjects, are plotted in Figs. 6 and 7, respectively. The plotted times are proportionate, and the 4 determinations done for each woman are identically numbered, as described for Fig. 5. We are well aware of the fallacy, emphasized by Frank,¹⁶ of judging the hormone excretion of an individual from isolated twenty-four-hour urine specimens during the menstrual cycle. Therefore, we shall not attempt to

uterus, may be of interest. This comparison arose from our original intention to use pitocin as the logical oxytocic agent for the above studies. However, this idea was abandoned when we found that in some cases in which pitocin had no effect on uterine motility, an injection of pituitrin given fifteen minutes later did cause increased contractions. This never occurred when the primary injection was either pituitrin or pitressin.

Thirty-seven tests of pitocin were made (as described for pituitrin) in our 15 normal subjects, using 1 c.c. (10 international units) intramuscularly in place of the first injection of pituitrin. Of the 16 injections given during the first half of the cycle, 7 resulted in increased uterine motility while 9 did not. Of the 14 tests made before the last two days of the second half of the cycle, 2 showed increased contractions while 12 did not. Of the 7 trials during the forty-eight hours preceding the next menstrual cycle, 3 yielded increased motility while 4 did not.

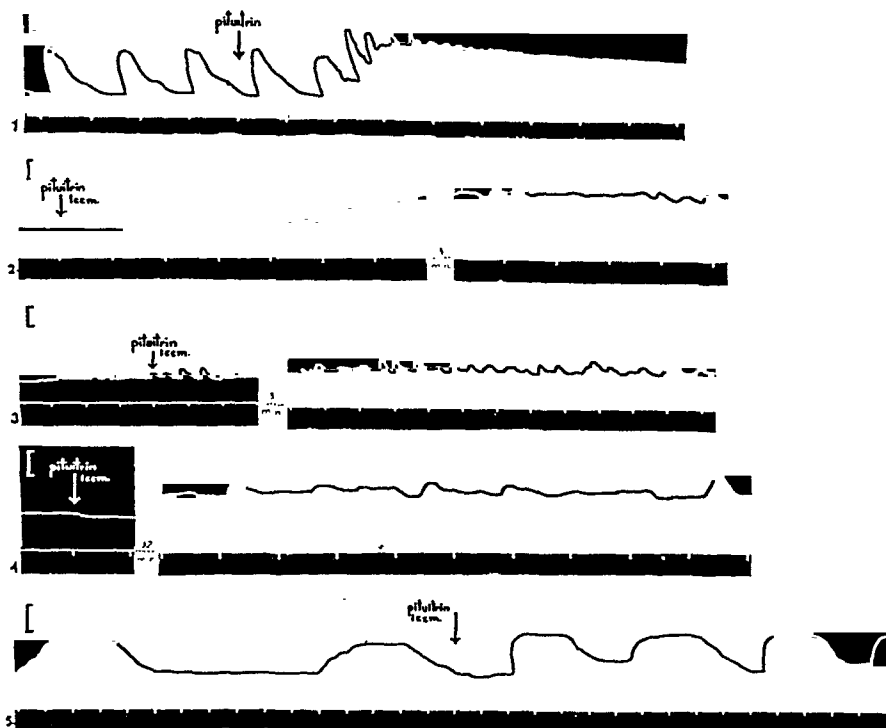


Fig. 4.—Composite of results from 5 different women, showing increased uterine motility after pituitrin administration at various times in the menstrual cycle.

Record 1: Mrs. S. A., aged 34 years; 4th day of a 26-day cycle
 Record 2: Mrs. S. S., aged 28 years; 13th day of a 34-day cycle
 Record 3: Mrs. V. W., aged 28 years; 16th day of a 29-day cycle
 Record 4: Mrs. K. K., aged 42 years; 26th day of a 30-day cycle
 Record 5: Mrs. E. S., aged 25 years; 24th day of a 26-day cycle

Conventions as for Fig. 1.

The severe systemic reaction, including abdominal cramps and tingling at the fingertips, which followed the injection of 1 c.c. (20 units) of pitressin, limited the number of cases in which it could be tried. Ten records were obtained from 8 of our subjects. Of the 5 tests made during the first half of the cycle, 3 resulted in increased uterine motility while 2 did not. Pitressin had no effect in the 5 trials made during the second half of the cycle.

Table I summarizes and compares the relative effectiveness of pituitrin, pitressin, and pitocin, in causing increased uterine motility during the different stages of the menstrual cycle. It may be seen that none of these preparations act in the manner described by Knaus. Strangely enough, it is the blood pressure-raising principle, rather than the oxytocic, which most nearly approaches his results. However, our data on pitressin are insufficient to warrant definite conclusions.

draw any conclusions from the variations in excretion of any single one of our cases. But since our method of presentation of these data tends to compensate for individual peculiarities, the general trend of our results as a whole should be a good index of the normal pattern of hormone excretion. According to the results of Kurzrok, and others,¹⁹ and Frank,¹⁰ we should expect to find a grouping of high values for prolan excretion at or about the middle of the cycle (Fig. 6). According to the same authors, we should also expect to see certain peaks in the values for estrin excretion about the middle and toward the end of the cycle (Fig. 7). However, neither of these tendencies is clearly visible in our graphs. It must be concluded that, even though certain normal women display the characteristic cyclic variations in hormone excretions described by some authors, many normal women do not follow the same pattern. These results should make one reluctant to infer the presence of a hormonal abnormality from urinary assays, unless the values obtained are significantly above or below the entire range of values ordinarily found in normal women during the menstrual cycle.

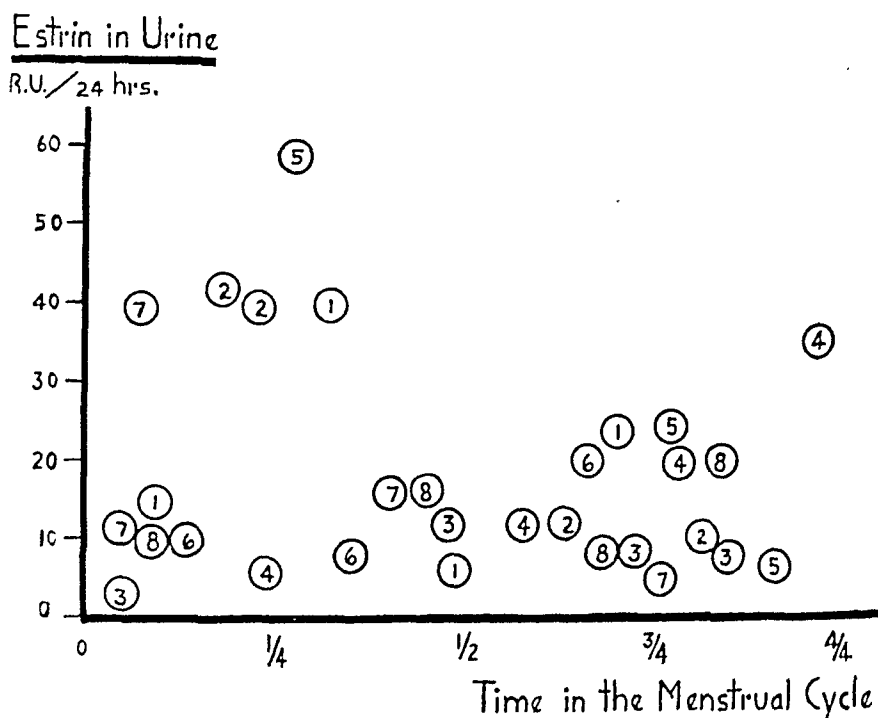


Fig. 7.—Quantitative daily estrin excretion observed once in each quarter of the menstrual cycle, in each of 8 normal women. Conventions as for Fig. 5.

SUMMARY AND CONCLUSIONS

A number of the important aspects of the menstrual cycle have been studied, throughout the cycle, in 15 normal women. The phenomena observed included the spontaneous motility of the uterus, uterine response to the administration of preparations of the posterior pituitary gland, changes in the uterine endometrium, and the urinary excretion of prolan and estrin.

The outstanding observation made during this work has been the irregularity of the above phenomena in various normal women, and their unpredictability for any given normal woman. In other words, while the above phenomena tended to follow certain behavior patterns, the number of exceptions was so great as to preclude the use of these phenomena as reliable criteria of normal sex function.

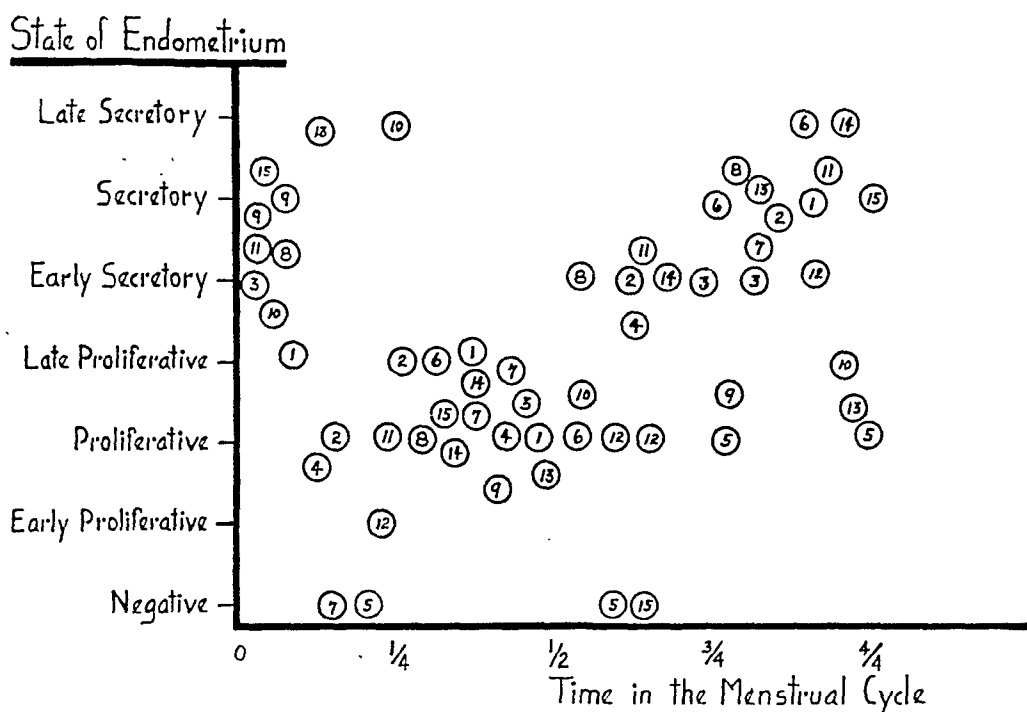


Fig. 5.—Histologic state of uterine endometrium, observed once in each quarter of the menstrual cycle, in each of 15 normal women. The 4 observations on each woman are identically numbered. The time of each observation is plotted as a proportion of the length of the menstrual cycle in which it was made. All the results are therefore comparable as to time. Zero time represents the day of onset of the menstrual flow.

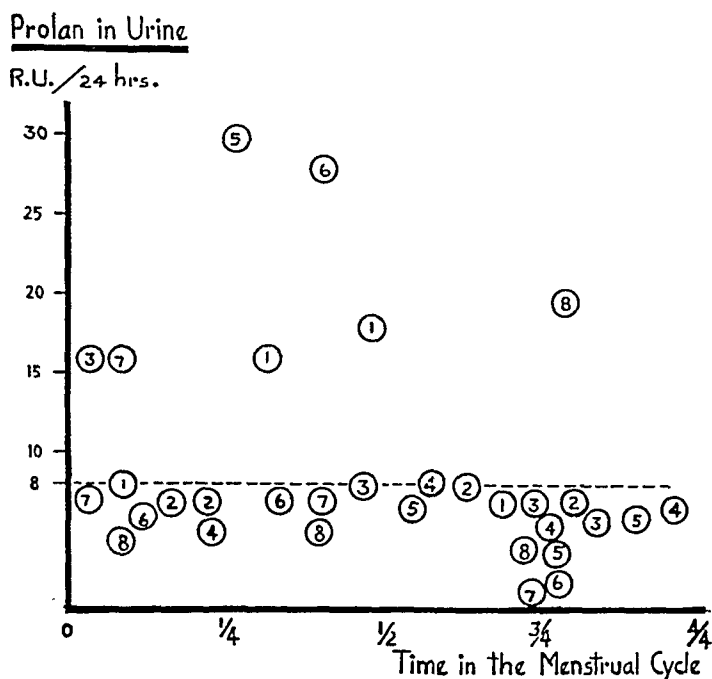


Fig. 6.—Quantitative daily prolactin excretion observed once in each quarter of the menstrual cycle, in each of 8 normal women. Since the minimum range of our prolactin assay was 8 rat units, the position of the plotted points below the horizontal broken line does not have any quantitative significance other than "less than 8 rat units per twenty-four hours." Other conventions as for Fig. 5.

must be somewhat different than in the case of nonspontaneously ovulating animals. These species variations must be considered in the interpretation of experimental procedures and results.

Allen, Burr and Musselman, and other workers have provided us with a new method for determining the time of ovulation. Their potentiometer which records minute changes in electrical potentials occurring in tissues may provide us with an instrument for accurately recording the time of ovulation. This method is still too complicated for clinical use, but it offers considerable possibility for future work.

Dr. Adair and I have been interested in the study of uterine motility for many years. In 1935 we reported the results obtained in the use of various oxytocic agents. We found that the two fractions of the posterior pituitary exhibited marked oxytocic activity when given to women in the immediate post-partum period by the intravenous route. Pitressin and pitocin exhibited almost equal oxytocic activity.

DR. EUGENE M. K. GELLING.—The hormones from the posterior portion of the hypophysis are among the most powerful ones in the body. One of the reasons we have not been able to isolate them is because of the extreme difficulty of getting sufficient material to work with. One begins to wonder, however, what is the function of these posterior lobe principles. In a series of hypophysectomized animals, it was recently found that the animals ovulated quite normally.

It is very dangerous to compare results in animals with those on human beings. We may have to start from the beginning in this matter of ovulation and make deductions from experiments conducted on the normal human being alone.

DR. LACKNER (closing).—This work was done on normal women in contradistinction to the work on the postnatal cases, and not on pregnant women, so perhaps the effect on the pregnant uterus is different from that on the nonpregnant uterus. I have just a few figures I would like to mention. We were somewhat astounded by the effect of pitressin. In 37 cases, 12 reacted to pitressin and 25 did not. However, in these same 37 cases in which we used pitressin, 31 reacted to pituitrin. There is, therefore, a decided difference between the effect of pitressin and pituitrin, which is manifested as a more pronounced reaction with pituitrin.

Rodecurt, Von M.: Examination of Smears of Operative Cases for Trichomonads, Ztschr. f. Geburtsh. u. Gynäk. 115: 99, 1937.

Rodecurt believes that the ascension of trichomonas may be responsible for many of the pelvic infections and adhesions of unknown origin. The organisms can be found in cultures of pus from the tubes as well as adnexal tumors. Wagner and Hess have found the organisms in ascitic fluid, in placental tissue of abortions, in the walls of ovarian cysts, as well as in an abscess of the abdominal wall one week after the removal of an ovarian cyst. Rodecurt believes that stained smears are satisfactory if enough smears are examined before considering a result negative. He secured positive smears from curettings, fibromyomas, ovarian cysts, pus tubes, tubal pregnancies, in the appendix, and in normal placentas, but was unable to recover the organism from the blood stream or the nasal secretions. On the other hand, Wagner and Hess were able to culture trichomonads from the blood stream in 55 instances. The author believes that the *Trichomonas vaginalis* has a facultative pathogenicity and does not necessarily cause acute symptoms. When the organism is the only one found in specimens, it could be assumed to be the cause of the infection. Thus the author concludes: that the trichomonas may cause malignant degeneration in an originally benign tumor, that it may be the source of post-partum infections as well as peritoneal adhesions, that it may be responsible for many cases of tubal pregnancy if the tubes have been damaged by the organism, and that also unexplained abortions may be due to infection with this organism.

EUGENE S. AUFE.

The results obtained from the administration of posterior pituitary preparations do not agree with those of Knaus from which he concluded that there was a single regular ovulation time for normal women. Either his test is highly unreliable, or normal women (in this country at least) ovulate at widely differing times in the menstrual cycle. In either case grave doubt is cast upon the Ogino-Knaus theory of the so-called "safe period."

A comparison of the relative effectiveness of pituitrin, pitocin, and pitressin in causing increased uterine motility, showed that the supposedly pure oxytocic principle was less effective than the mixture composing obstetric pituitrin. Pitressin has potent oxytocic properties, *in vivo*.

As regards the urinary prolactin and estrin, since no regular pattern of excretion during the menstrual cycle was found, it is concluded that extreme caution should be exercised in the interpretation of such assays, unless the amount of hormone excreted is significantly above or below the entire range of values found during the menstrual cycle of normal women.

We are greatly indebted to Dr. S. Charles Freed for his cooperation in assaying our many samples of urine for prolactin and estrin content, and to Dr. Otto Saphir for his interpretation of our histologic preparations.

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DISCUSSION

DR. M. EDWARD DAVIS.—Dr. Lackner and his associates presented the results of their experiments on the Ogino-Knaus concept for determining the time of ovulation. Their results add additional proof to many previous experiments which disagree with this concept. It is unlikely that variations in uterine motility occurring at various periods during the normal menstrual cycle can be regarded as solely due to endocrine factors. Others factors must necessarily influence these changes. Smooth muscle normally contracts spontaneously. Furthermore, the intact uterus has both an intrinsic and extrinsic innervation.

The Ogino-Knaus experiments have been confirmed largely on laboratory animals, particularly the rabbit. One must remember that ovulation in the rabbit does not occur periodically of its own accord, but follows copulation or mechanical stimulation of the reproductive tract. In women ovulation occurs periodically as part of the normal cyclical changes. The mechanism for the production of ovulation in women

Croom noted in Edinburgh that the incidence of eclampsia was highest in very cold, rainy weather, during which the relative humidity was very high. The incidence of eclampsia is greater in England and Ireland than it is on the continent of Europe.

Küstner stated that the highest incidence of eclampsia was in the spring and late summer and suggested that the ultraviolet radiation might be a factor.

Merletti and Grappa stated that a correlation existed between the incidence of eclampsia, changes in barometric pressure and humidity.

Kosmak reported some work of Harrar's which indicated that over a ten-year period the number of cases of eclampsia in the Lying-in Hospital in New York was greatest in March, April and May. The weather in these months is cold, damp and unsettled.

Hauch and Lehmann have made a thorough study of eclampsia in Denmark and have been able to account almost entirely for some of the peculiarities about its occurrence. Since their data are so complete and have been so carefully analyzed we include them to demonstrate how more than one factor may explain an alteration in the incidence of eclampsia and how carefully statistics must be interpreted. The decreased occurrence of eclampsia during the war in Germany and also in Denmark has been attributed to the lack of protein and fat in the diet and the increased work of the women, resulting in better oxidation of the food. However, these authors noted that the drop in the frequency began in 1915 before there was any lack of food and the great rise in incidence began at once in 1919 and reached its first maximum in 1921, when the condition of nutrition, as far as the majority of the population was concerned, had not changed materially. They attributed these changes to the marriage rate in nulliparae. The curve for the incidence of eclampsia and percentage of primiparae parallel each other. They believed that a change of income rather than food or mode of living was the predominant factor. During the war the income was low and therefore the number of marriages, which are chiefly of nulliparae and, therefore, if pregnancy occurs, more likely to have eclampsia, was decreased. After the war, the number of marriages increased and the incidence of eclampsia rose.

Hauch and Lehmann have also noted that there are more cases of eclampsia in March and August, and they attribute this to the fact that most marriages in Denmark occur in May and November, thus producing a 9- to 10-month interval. They also find that the incidence of eclampsia in Copenhagen is 0.31 per cent, in provincial towns 0.18 per cent, and in rural districts 0.10 per cent. They attribute this difference in part at least to a difference in the fertility of the women in the different locations. The annual number of births per 100 women between 16 and 49 years was thus: in the capital 10.4, in the provincial towns 14.2, and in the rural districts 17.5, despite a greater frequency of marriages in the towns. The annual number of marriages per 10,000 inhabitants was: in the capital 100, in the towns 82, and in the country 69. Fertility also decreases at a higher rate with increasing age within the urban population. Therefore, it can be assumed that there is a relatively greater number of primiparae, and thus younger women, among the childbearing women of the cities, thus accounting for the increased incidence of urban eclampsia.

Scheyer reviewed the incidence of eclampsia in Canton, China, and found that the largest number of cases occurred in September, December, January, and May, and the greatest number of patients with preeclampsia were found in July, August, and September. He attempted to correlate his findings with the meteorologic conditions but found it very difficult to do so.

Tottenham has studied the seasonal incidence of eclampsia in Hong Kong and noted that 66 out of 97 cases of eclampsia occurred during the months of September to February, inclusive. During this period the humidity is always below 80 per cent

THE GEOGRAPHIC DISTRIBUTION AND EFFECT OF CLIMATE ON ECLAMPSIA, TOXEMIA OF PREGNANCY, HYPEREMESIS GRAVIDARUM, AND ABRUPTIO PLACENTAE

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THESE diseases occur only in the pregnant woman and the incidence for them should be approximately the same irrespective of race, climate, diet, or habits if they are caused by the pregnancy per se. However, if the occurrence varies in different countries, then the pregnancy is just one factor and if the other factors can be determined, studies may then be made to eliminate them and thus prevent the occurrence of these diseases.

Various authors of textbooks, in discussing the etiology of eclampsia, have stated that the disease is uncommon or rare in the tropics. The majority of them have ascribed the low incidence to the diet which they assumed to be mainly carbohydrate. So far as we know, they have cited no authorities or statistics for their statements.

Dass, in 1895, published an excellent review of eclampsia. He stated that Smellie, Lever, Simpson, and many other obstetricians had noted some periodicity in the occurrence of the disease, but no one had an explanation for it. Spiegelberg suggested that the quasi-epidemic occurrence of eclampsia might be brought about by "atmospheric influences, specially affecting the skin, an organ whose relations to fetal activity are, of course, well known." Dass thought that the high incidence of 0.94 per cent might be due to the sudden alterations in temperature and humidity which occur so frequently in Calcutta. His data also seemed to indicate that early childbearing was a distinct predisposing cause.

Because of the varied incidences of eclampsia Theobald believes that it cannot be caused by a placental toxin or by any functional or organic lesions in the kidneys. He states that from the known facts about eclampsia, together with his own experimental data, one is justified in stating that the disease is caused by toxins absorbed from the intestinal canal which, owing to a breakdown in the defenses of the body, are not detoxicated. He suggests that a deficiency of ionized calcium in the blood is the cause of the breakdown of the defenses of the body.

Buck noted that 320 cases of eclampsia out of 340 occurred during changeable weather.

Sachweh noted that the majority of 118 cases of eclampsia occurred in moist and especially moist and warm weather.

Von Heuss, in his series of 1,700 cases of eclampsia, noted that the attacks were especially started by summer thunderstorms and the "cold waves" which accompanied these.

country as a whole, but in many of the foreign cities, only hospital statistics are available. We are also cognizant of the fact that the number of hospital deliveries in foreign countries is proportionately small as compared to all the deliveries, in contrast to the large cities in the United States where hospital deliveries form the major part. Furthermore, in India, China, etc., only patients with difficult complications are admitted to the hospital.

The meteorologic data have also been obtained for the various cities. The daily mean, maximum and minimum, temperature and inches of rainfall can be obtained for all cities in the United States but, as a rule, only the annual figures are available for foreign cities, especially those in Asia, Africa, and the islands.

The data for Europe and the British Isles are listed in Table I. The incidences for the latter are all from hospitals in London, Manchester, Dublin and Glasgow. Not only do these diseases occur more frequently here but the mortality due to them is much greater than that of any other country. We have no explanation for this, but believe it should be investigated further.

TABLE I. OCCURRENCE OF ECLAMPSIA IN EUROPE

PLACE	MATERNAL MORTALITY %	ECLAMPSIA INCID. %	NONCONVUL- SIVE TOXEMIA INCID. %	HYPER- EMESIS GRAVIDARUM INCID. %	ABRUPTIO PLACENTAE INCID. %
England	1.94	1.61	8.02	2.24	2.79
Scotland	1.47	1.63	-	2.11	2.42
Ireland	0.58	0.61	16.60	0.55	0.84
Germany		0.39	4.40	1.00	0.94
France		0.58			
Sweden		0.38			
Finland		1.20			
Denmark		0.86			

The incidence of these various diseases for the native population in other countries is listed in Table II. If data from several hospitals in the same city or from nearby towns were obtained, they were grouped and an average calculated.

Data were collected from 40 cities in the United States but only representative figures from various parts of the country are listed in Table III. The marked variation in the occurrence and mortality of these diseases, under supposedly ideal conditions, is noteworthy. What is the cause of the difference in mortality for eclampsia and toxemia? Are these diseases more severe in the South than in the North? Do the patients have less resistance? Is prenatal care more intelligently administered? Or is the method of treatment better in some cities? Similar questions are pertinent for hyperemesis gravidarum and abruptio placentae. More data must be collected before these questions can be answered.

Table IV lists the means for the incidence of eclampsia, etc., in the various countries. These figures are based on the data collected. The incidence of eclampsia for the world, based on our figures, is 1.0 per cent. The difference in the occurrence of these diseases of pregnancy between the British Isles and the United States is striking, and questions similar to those in the preceding paragraph are pertinent.

whereas in the remainder of the year it is over 80 per cent. During this same period the temperature is at its minimum. Because of the small series he was unable to draw any definite conclusions.

Titus attributed the low incidence of eclampsia among the Eskimo to the fact that the temperature of their country is always low and constant. Thus, despite a high protein and fat diet, which presumably is a factor in causing eclampsia, these people are not subjected to sudden changes in the weather.

Harding and Drew stated that eclampsia is most frequent in Toronto, Canada, from November on, reaching a peak in March.

For several years we kept a record of the daily temperature, barometric pressure and humidity but the number of cases of eclampsia in our hospital was too small to enable us to draw any conclusions. However, we have repeatedly seen eclampsia occur when an abrupt change in the weather took place. The change might be from hot to cold or vice versa. We have also noted in the Toxemia Clinic that toxemic patients whom we have been following from week to week usually have their symptoms intensified when one of these abrupt changes occurs. If one could have available the records of all toxemic patients for a city of several million people together with the meteorologic data, we believe a very definite correlation would be found for the occurrence of eclampsia and abrupt alterations in the weather. These changes in the weather are certainly not the cause of the eclampsia but in susceptible patients these sudden alterations may cause disturbances in the water balance, acid-base equilibrium, and vascular system which result in intensifying the hypertension, edema, oliguria, etc., until convulsions and coma occur. Smith has reported that there is a water retention in the bodies of dogs and rats when the barometric pressure is lowered from 3 to 10 cm. of mercury during a period of from 12 to 48 hours. This disturbance of water balance is accompanied by restlessness.

We have collected data as to the occurrence of eclampsia, nonconvulsive toxemia, hyperemesis gravidarum and abruptio placentae from various parts of the world. Cases of abruptio were included because in a high percentage of the cases hypertension is also present. Hyperemesis was included because although it is not a toxemia yet it is a condition peculiar to pregnancy. Some of the material was obtained by a page-to-page study of all of the foreign journals at the American Medical Association Library for at least a 5-year period. Hospital reports were collected. One hundred and twenty questionnaires were sent to foreign hospitals and missionary doctors and 80 to hospitals in the United States. With but few exceptions everyone returned the form, either with their data or a note as to why they could not supply them. We asked for a 5-year summary, showing the annual number of deliveries, the number of patients with eclampsia, toxemia, hyperemesis, and abruptio, and the total and group maternal mortality. We realize that the hospital incidence of a disease is greater than for the

TABLE IV

PLACE	NUMBER OF DELIVERIES	INCIDENCE OF—PER CENT			
		ECLAMPSIA	NON-CONVULSIVE TOXEMIA	HYPER-EMESIS GRAVIDARUM	ABRUPTIO PLACENTAE
United States	276,221	0.66	4.13	0.87	0.54
British Islands	99,253	1.13	10.88	1.48	1.82
Europe		0.68	*4.40	*1.00	*0.94
Asia, Africa, etc.	1,876,961	0.52	0.52	0.19	0.17
Mean for all data		1.00	5.10	0.89	0.87

*One German Clinic.

Our figures for many of the hospitals in Asia, India, Africa, etc., are really not comparable to hospital figures for the United States. There is no prenatal care, and hospital beds are few in number. Thus there occurs the paradox of a lower incidence for nonconvulsive toxemia than for eclampsia. As to hyperemesis gravidarum, only the seriously ill patients would be hospitalized. Abruptio placentae is quite often grouped with placenta previa, and, furthermore, many cases were either not correctly diagnosed while at home or died before they could be taken to the hospital. For these various reasons and because convulsions and edema in the pregnant woman are striking signs, eclampsia was selected as the index for study.

The data from the various countries are of great interest. Eclampsia, toxemia, hyperemesis, and abruptio are either unknown or are very rare among the native women of Kenya, Uganda, the Zulu, Tanganyika, Belgian Congo, Ethiopia, Persia, Java, Hawaii, British Malaya, Alaska, Australia, and date oases of Africa whose habits and diet have not been changed by the white race. In contrast, eclampsia is very common in Algiers, Cape Town, Colombo, and Porto Rico, where the natives have adopted many, if not all, of the diet and other habits of the white. Eclampsia is very rare among the negroes in Africa, but has an incidence among the negroes of 0.71 per cent in New Orleans and 0.92 per cent in Atlanta. Of course, the negro in this country is not of pure strain, but these figures do show the effect of a different diet, habits, climate, etc. Hypertension is also rare in the African negro male and female in contrast to its high frequency in the colored race in this country.

Similarly, eclampsia is uncommon or rare in the country districts of India and China in contrast to the cities where it is very common. Again the chief factor seems to be the adoption by the natives of the habits and diet of the white.

We have been able to gather some statistics as to the incidence of eclampsia during the last century.

Rotunda Hospital, 1826 to 1833: Collins reports 16,654 deliveries with 39 cases of eclampsia, an incidence of 0.18 per cent and mortality of 17 per cent.

TABLE II. OCCURRENCE OF ECLAMPSIA IN THE NATIVES OF VARIOUS COUNTRIES

PLACE	MATERNAL MORTALITY %	ECLAMPSIA INCID. %	NONCON- VULSIVE TOXEMIA INCID. %	HYPER- EMESIS GRAVI- DARUM INCID. %	ABRUPTIO PLACENTAE INCID. %
Algiers, Africa	--*	2.85	--	--	--
Cape Town, Africa	--	1.44	--	0.04	1.60
Tanganyika (etc.), Africa	3.80	0.10	0.13	0	0.03
Zulu, Africa	--	Very rare	Rare	0	0
Ethiopia	--	0	Rare	Rare	0
Belgian Congo, Africa	--	0	--	Rare	--
Colombo, Ceylon	3.90	2.76	2.93	0.21	1.40
Porto Rico	--	2.54	27.33	0.25	0.33
Shanghai, China	1.97	1.27	3.31	0.22	0.83
Hong Kong, China	0.40	0.92	0.42	0.0001	0.31
Virgin Islands	0.39	1.25	0.26	0.26	0.46
Japan	--	1.16	--	--	--
Philippine Islands	2.62	1.03	0.16	0.27	0.18
Bangkok, Siam	2.21	0.68	2.87	0.59	0.23
Fiji Islands	--	0.63	--	--	--
Trinidad	--	0.23	19.00	--	--
New Zealand	--	0.20	2.09	--	0.57
Persia	2.60	0.19	0.46	Rare	0.19
Java	--	0.18	--	--	--
Hawaii	--	0.15	5.00	--	--
British Malaya	0.65	0.04	0.05	--	0.05
Alaska	--	0	0	--	--
Australia	--	0	0	0	0

*--, No data given. 0, No cases.

TABLE III. OCCURRENCE OF ECLAMPSIA IN THE UNITED STATES

PLACE	ECLAMPSIA		NON- CONVULSIVE TOXEMIA		HYPER- EMESIS GRAVIDARUM		ABRUPTIO PLA- CENTAE	NUMBER OF DELIVERIES
	INC. %	MORT. %	INC. %	MORT. %	INC. %	MORT. %	INC. %	
Charlotte, N. C.	7.2	5.6	29.40	---	---	---	---	500
Charlottesville, Va.	2.25	17.3	9.94	3.5	3.03	1.4	1.43	2,314
Charleston, S. C.	2.23	14.0	4.87	10.0	0.66	10.5	0.10	2,873
New Orleans, La. (White)	1.62	25.5	---	---	2.89	2.3	---	2,903
New Orleans, La. (Negro)	0.71	30.7	---	---	1.24	5.9	---	5,456
Los Angeles, Calif.	1.12	14.5	5.40	3.3	2.12	1.9	1.27	9,865
Atlanta, Ga. (Negro)	0.92	6.9	8.50	0.2	0.18	---	0.72	7,799
Texas	0.50	19.0	1.45	2.9	0.21	6.7	---	9,310
Johns Hopkins	0.80	6.8	23.30	0.9	0.11	---	0.49	5,519
Pittsburgh, Pa.	0.59	21.8	1.58	10.4	1.35	5.2	---	25,300
Detroit, Mich.	0.56	5.9	3.40	2.6	0.04	---	0.87	9,118
Jersey City, N. J.	0.49	8.7	6.96	0.6	0.20	---	0.46	9,438
St. Louis Maternity	0.42	17.0	3.35	0.4	1.15	---	0.08	7,689
Milwaukee, Wis.	0.41	4.2	1.02	1.0	0.85	4.1	0.48	5,781
Philadelphia, Pa.	0.40	10.0	0.19	1.4	1.02	2.6	0.37	7,503
Chicago Lying-in	0.35	5.8	7.21	1.2	0.24	5.4	0.37	14,864
Cleveland, O.	0.29	---	9.41	---	0.60	---	0.87	9,274
Great Falls, Mont.	0.24	40.0	0.24	0	0.83	---	---	2,045
Lincoln, Neb.	0.06	---	2.93	---	1.91	---	---	1,675

Dr. Randall summarizes as follows: "It appears from the above coefficients that the only factor of possible significance is the average temperature. All of the coefficients, however, are small; further data are obviously required before any stable relationships could be shown. The climate which would seem to be most favorable to the incidence of eclampsia, on a basis of these data, would be one with a high average temperature, a small range of temperature, and a high measure of rainfall—in other words, a hot wet climate."

Meteorologic conditions are not the only factors. The following table taken from Balfour's report illustrates that under the same conditions of climate and temperature other factors, such as race, diet and domestic habits, cause marked differences in the occurrence of eclampsia.

	BOMBAY HOSPITALS		ALL INDIA HOSPITALS (LESS BOMBAY)	
	NO. OF CASES	INCIDENCE OF ECLAMPSIA %	INCIDENCE OF ECLAMPSIA %	NO. OF CASES
Hindu	2,066	0.38	1.52	5,167
Mohammedan	842	1.66	2.43	1,273
Christian	801	0.37	0.69	1,152

These are, of course, all hospital statistics, but the differences between Hindu, Mohammedan, and Christian are so great that one must conclude that they are significant. The most likely explanation of the greater incidence is that the diet of the Mohammedan contains meat in contrast to that of the Hindu who eats no meat.

Our data also indicate that the race, diet, and personal habits are all of importance when one considers the incidence of these various diseases. It is obvious that until we eliminate these other factors we must acknowledge the fact that Randall's remarks as to temperature and rainfall, which are based on statistics, cannot be regarded as conclusive.

Another pertinent observation is the appallingly high maternal mortality in Africa, Ceylon, India, China, Siam, etc., and what is most remarkable is the fact that the maternal deaths are not due to eclampsia and toxemia. In the United States these two diseases account for 20 to 40 per cent of the maternal deaths, but in the countries listed above, either they are not the cause or the percentage of total deaths caused by eclampsia and toxemia ranges from none to 10 per cent. Vital statistics are notoriously open to error but convulsions, pregnancy, and death are a triad which should be easily recognizable. Therefore, the very fact that toxemia deaths not only form a small part of the total maternal mortality, but are few in actual numbers in Asia, Africa, etc., gives additional confirmation to our data as to the occurrence of eclampsia.

Churchill in 1843 collected 159 cases of convulsions in 96,903 labors, an incidence of 0.16 per cent. The maternal mortality ranged from 28 to 70 per cent.

Medical College and Eden Hospitals, Calcutta, 1848 to 1894: Dass reported 10,728 deliveries with 101 cases of eclampsia, an incidence of 0.94 per cent and mortality of 58 per cent.

Many similar figures are available. Eclampsia is probably not increasing. For example, Hauch and Lehmann reported an incidence of 0.10 per cent for rural eclampsia in Denmark between 1918 and 1927. Hinselmann states the incidence in Germany among patients at home is 0.05 per cent. Thus, the figures for the last century, when hospital delivery was rare, are comparable to modern statistics of home delivery.

Dr. William Randall of our Graduate Library School has made a statistical analysis of our meteorologic data and the incidence of eclampsia. Correlation coefficients were figured for the following variables, with the accompanying results:

FOR THE TOTAL STATISTICS

Incidence of eclampsia/average temperature	0.344 \pm 0.069
Incidence of eclampsia/range of temperature	-0.240 \pm 0.076
Incidence of eclampsia/rainfall	0.160 \pm 0.076

The first of these is significant and indicates that temperature is a factor in the occurrence of eclampsia.

Partial correlation coefficients were figured for the incidence of eclampsia against each of the other three variables, holding the two extra variables constant, with the following results.

I.Ec./Average temperature (range and rainfall constant)	0.285
I.Ec./Range of temperature (average temperature and rainfall constant)	0.66
I.Ec./Rain (average temperature and range constant)	-0.114

The first of these has some significance.

FOR THE UNITED STATES ONLY

Incidence of eclampsia/average temperature	0.442 \pm 0.086
Incidence of eclampsia/range of temperature	-0.377 \pm 0.091
Incidence of eclampsia/rainfall	0.198 \pm 0.102

The first and second are significant, but again temperature is the predominant factor.

Partial correlation coefficients for the United States:

I.Ec./Average temperature (range and rainfall constant)	0.247
I.Ec./Range of temperature (average temperature and rainfall constant)	-0.004
I.Ec./Rain (average temperature and range constant)	-0.083

The first of these has some significance.

Multiple correlation coefficients were figured to determine the chance of predicting the incidence of eclampsia on a basis of the three variables, with the following results:

Total statistics	0.336
United States only	0.450

These figures indicate that if we knew the meteorologic data for a city, one could predict the probable occurrence of eclampsia and for the world be correct in about 11 per cent and for the United States in about 20 per cent of the cases.

CONGENITAL ABSENCE AND TRAUMATIC OBLITERATION OF THE VAGINA AND ITS TREATMENT WITH INLAYING THIERSCH GRAFTS*

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CONGENITAL absence of the vagina results from faulty development or fusion of the Müllerian ducts. Variations in the development of this defect are designated as aplasia, atresia, hypoplasia, and duplication. There may also be various combinations of these states. With entire absence of the vagina there is usually an associated absence or arrested development of the uterus and, not infrequently, of the adnexa. The entire vagina is represented by a fibrous or fibromuscular cord situated between the bladder and the rectum, the uterus usually being maldeveloped, often solid and divided into two parts.

Not all patients who have congenital absence of the vagina should be treated surgically, but only those who are otherwise normally developed and who contemplate marriage. Some patients without a vagina also are without ovaries and therefore show an abnormal balance between prolactin and estrogenic hormone and an associated sexual indifference. Patients who are normal in every other respect but who do not contemplate marriage need not be treated since their health will not be affected by the defect. When patients have married before the existence of the defect became known surgical reconstruction is of course essential. The psychologic basis for surgical interference in such cases is important. In many instances a sex neurosis develops when the patient learns of her condition and she feels she will never be able to take her normal place in society. Occasionally such a patient has resorted to suicide during a period of mental depression. A thoughtful discussion of the subject, in which it is clearly stated that the anomaly is not at all uncommon and can be corrected surgically, does much to appease this mental distress.

Traumatic stricture of the vagina, either partial or complete, is occasionally seen following difficult instrumental delivery incident to extensive sloughing of the vaginal mucosa. It also occurs from external violence, in which case the perineum and rectum may also be injured. In these cases the birth canal and menstrual function have been normal and surgical reconstruction is definitely indicated. If associated injuries to the bladder, urethra, and rectum have also occurred, producing fistulas, surgical reconstruction is necessarily divided into stages and the first stage consists of closing the fistulas and obtaining a continent bladder and rectum.

SUMMARY

The geographic distribution of eclampsia, toxemia of pregnancy, hyperemesis gravidarum, and abruptio placentae has been studied. These diseases are peculiar to pregnancy and the incidence should, therefore, be constant throughout the world.

Eclampsia, because of its striking symptoms and signs, has been used as the index. Collected data show that the incidence ranges from 0 in many cities to 2.85 per cent in Algiers, Africa, and 7.2 per cent in Charlotte, North Carolina. The mean incidence for the world is 1.0 per cent, for the United States 0.66 per cent, for the British Isles 1.13 per cent, for Europe 0.68 per cent, and for the rest of the world 0.52 per cent.

The incidence of eclampsia and meteorologic data for various cities have been studied statistically. There is some correlation, especially for the United States, between eclampsia, a high average temperature, a small range of temperature, and a high measure of rainfall.

Our data seem to indicate that eclampsia may and undoubtedly does occur in the native who has had little or no contact with modern civilization. However, the latter with its mental strain and stress, change in diet and habits seems to cause an increase in the occurrence of eclampsia.

Our results warrant further investigation of the geographic distribution of these diseases, as a means of, first, determining pertinent factors, second, eliminating or preventing them, and third, determining their relation to the etiology of the disease in question.

I wish to thank the various doctors, hospital superintendents, and public health officials who cooperated so generously. I appreciate the courtesy shown me by the librarian of the American Medical Association. Dr. R. B. Michener, Kenya, Africa, was most helpful in the collection of data from East Africa.

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for several weeks. At the end of this period the mold could be removed and the vaginal canal was at this time completely covered with a thin layer of epithelium and closely resembled a normal vagina in every respect. Although Kirschner and Wagner and others in Germany who used a similar method had reported excellent results in most cases, there were a few cases in which contraction later produced some difficulty. They emphasized the point, however, that dilatation should be continued by the patient for a considerable time. The entire procedure was performed in one stage and the period of hospitalization rarely exceeded three weeks. The surgical risk was also reduced to a minimum.

In order to overcome the inconvenience to the patient which is caused by the necessity of wearing a vaginal dilator constantly, McIndoe recommended complete closure of the vulva over the mold and skin graft, but provided a small opening in the perineum for drainage. At the end of a six-months' period the contraction phase had passed and the vulva could be opened and the mold removed without fear of secondary contraction. He claimed no inconvenience to the patient from keeping the mold in position in this manner.

I have further modified this method by utilizing a flexible rubber tube, over which the graft is placed, instead of a solid rubber mold. The rubber tube can be cut to any desired length, which is necessary because of the fact that the distance between the peritoneum and the peritoneal reflection is variable in cases of congenital absence of the vagina. In my method the rubber tube is removed in from ten to fourteen days and is replaced by a bakelite sound, which is made especially for each patient. A sanitary belt is worn by the patient; this belt fits firmly around the neck of the sound which maintains it in constant position. The sound is worn continuously for six months, being removed once a day for cleansing purposes.

In the past fifteen months I have used this method in five cases of congenital absence of the vagina and in two of stricture of the vagina following delivery, in all instances with good results. The skin grafts have been cut by my colleagues in plastic surgery, Dr. Figi and Dr. Havens.

REPORT OF CASES

CASE 1.—An unmarried girl, 17 years of age, came to the clinic on March 29, 1937, complaining that she had never menstruated. Two years previously she had begun to have periodic pelvic pains each month, and just before these occurred there was some headache and backache, and swelling and pain in the breasts. In December, 1935, she was examined and absence of the vagina was found. Reconstruction was attempted in January, 1936, elsewhere, but was not completed.

On examination at the clinic the patient weighed 119 pounds (54 kg.) and was of good physical development. Her breasts were firm and somewhat large for her age. The vulva and clitoris were normal but the vagina was only about $\frac{1}{2}$ inch (1.3 cm.) in length. Cystoscopic examination showed a rather large bladder with slight reduction in expulsive force. No abnormal openings could be demonstrated. Both ureteral orifices were somewhat gaping, but the urine from each side was normal. A diagnosis was made of congenital absence of the vagina. On April 5, the tissue between the bladder and rectum was separated up to the reflection of the peritoneum. An inlying split Thiersch graft was then placed in position after the method described. Ten days later the vaginal tube was removed and the grafts were inspected. The tube was replaced by a vulcanite splint, which was to be left in position for six months.

For more than a century, attempts at surgical reconstruction for congenital absence of the vagina and for atresia have been carried out by many different methods and with varying degrees of success.

The first good results were reported by Schubert and by Baldwin who utilized the large intestine. Schubert substituted the rectum for the vagina and reconstructed the rectum by bringing the bowel down and attaching it to the sphincter. Baldwin modified the procedure by bringing down a portion of the sigmoid colon, re-establishing intestinal continuity by end-to-end anastomosis. He later changed this method by bringing down a loop of ileum or jejunum, if the length of the mesentery did not prohibit. It has been observed by those who favor the Baldwin operation that it is unwise to place any undue tension on the vessels of the mesentery which supply the loop intended for the new vagina, since tension invariably leads to thrombosis and loss of vitality of the resected bowel. However, when sufficient length is available to bring the loop to the perineum and there are no other complicating conditions, this operation is one of the most satisfactory ones available for correction of the defect. Judin reported six successful cases in which the Baldwin technic was used without a death. I have personal knowledge of many other successful cases, but also of many failures which have not been reported.

Graves was one of the earliest writers to report good results from pedicle grafts taken from the labia and also from the skin of the thigh by a method which he originated. He reported five cases, covering a thirteen-year period in which patients had been so treated. Four of the patients had normal secondary sex characteristics. Since the labia in many cases are quite small, making it almost impossible to perform Graves' operation, modifications were advocated by Frank and Geist. They formed a tubular graft taken from the thigh and later placed it in the new vaginal site. Grad later introduced modifications of the tubular graft, the purpose of which was to maintain greater blood supply and thereby guard against later necrosis.

Although many good results have been reported following the use of these skin and pedicle grafts, they have many disadvantages, chief among which is subsequent secondary contraction which will invariably ensue unless some method is substituted to prevent it. This can be overcome, however, by constant dilatation during a period of four to six months, which can best be accomplished by a retained mechanical dilator. Another distinct disadvantage is the prolonged hospitalization and repeated operations necessary to correct the defect by multiple stage procedures. This entails considerable expense to the patient and furthermore makes it unwise for anyone to attempt the procedures if he is not familiar with plastic surgery and with the use of pedicle grafts.

McIndoe, who was cognizant of the disadvantages associated with pedicle grafts as a routine method and of the fact that the risk involved in using any part of the intestinal tract was perhaps too great to assume in correcting a defect which of itself was not a hazard to life, suggested a simple method of utilizing a large Thiersch graft taken from the thigh and implanting it into the vaginal position.

In brief this procedure consisted in first opening the space between the bladder and rectum up to the reflection of the peritoneum. This latter structure was then pushed upward to add depth to the new tract. A solid rubber mold was constructed to conform to the depth and diameter of the new vagina, which usually measured 4 by 1½ inches (10 by 3.8 cm.). A Thiersch graft of sufficient size to cover the rubber mold completely was then cut in one piece from the skin of the thigh. This graft was then sewed on the mold with catgut sutures. The mold carrying the graft was then carefully placed within the vaginal tract and held firmly in this position

On examination the patient's general physical condition was found to be good except that she was totally incontinent and there was considerable scarring of the perineum. Cystoscopic examination under anesthesia showed the urethra to be practically destroyed; the index finger could be inserted into the bladder through the site of the urethra. The sphincter was still present, although it was markedly weak. The bladder appeared normal and clear spurts of urine could be seen coming from both ureteral orifices. Pelvic examination at this time showed the posterior vaginal wall to be lacerated and healed by dense scar tissue, which narrowed and shortened the vagina. The cervix was not palpable and there seemed to be a small fistulous tract running up to it on the right side. Operation was advised but the patient deferred it.

One month later the patient returned to the clinic for surgical treatment. At operation, on August 17, I was able to separate the anterior vaginal wall up until I could feel the cervix through the tissues, although I could not find an opening into the cervix. The vagina, except near the cervix, had been obliterated by sloughing of the mucosa. About $1\frac{1}{2}$ inches (3.8 cm.) of the posterior vaginal wall near the cervix appeared normal. This was elevated and sutured to the skin of the labia minora. The vaginal canal was then packed with gauze, the urethra was partly reconstructed and one retention catheter was placed in the bladder. The patient was then given vaginal dilators and advised to use them daily, following her dismissal from the clinic, in order to overcome the contraction. The urethral sphincter became completely continent and she was able to void normally. The vagina, however, became practically occluded by scar tissue.

The patient was readmitted to the hospital on March 22, 1937, for reconstruction of the vagina. An inlying split Thiersch graft over a rubber tube was utilized after the method described. The bladder was again separated from the rectum by cutting through the scar tissue. At this time I was able to identify the cervix and the cervical canal. It was opened and the uterus was curetted. A Baldwin tube was then placed in the cervix and held in position by a silkworm suture. A split Thiersch graft was placed over a rubber tube, which measured 4 inches (10 cm.) in length, and this was fitted snugly into the vagina around the cervix and left in position for two weeks. Fourteen days later the Baldwin tube was removed because the patient was menstruating and the rubber tube was removed and replaced by a bakelite sound. The vaginal tract was almost completely epithelized except near the cervix on the anterior vaginal wall. The scar tissue to the left of the broad ligament remained somewhat sensitive and there was some constriction around the cervix. The patient has menstruated at regular intervals since, although she does have some pain. Her sex life is satisfactory, but she has been advised against further pregnancies.

CASE 7.—A married woman, 19 years of age, registered at the clinic on June 9, 1937, complaining of pain in the right side of her chest. On May 2 she had been delivered of a baby and following this had had chills and fever. She had been given four transfusions and intravenous medication. Blood cultures were negative. The patient had returned home but, after two days, sudden pain developed in the left side of her chest associated with coughing, chills, and fever. Her temperature was 106° F. The patient also complained of pain in the right lower abdominal quadrant.

The patient's general physical development was normal. No uterus could be felt on rectal examination, the clitoris was somewhat enlarged and there was an absence of the vagina. On June 29, an inlying split Thiersch graft was placed in position according to the method described. Ten days later the tube was removed and replaced by a bakelite vaginal dilator. The entire vaginal tract was completely epithelized. The patient returned to the clinic four months later, at which time the vagina measured 4 inches (10 cm.) in depth and $1\frac{1}{2}$ inches (3.8 cm.) in diameter with a normal introitus.

CASE 3.—An unmarried woman, 18 years of age, registered at the clinic on May 24, 1937. She said that she had never menstruated but that she had had periodic headaches each month and her breasts had become swollen. There was no abdominal pain at any time. She had been married only a few months when her marriage was annulled.

On physical examination at the clinic the patient was found to be well developed. Her breasts were normal in size. On rectal examination no pelvic organs could be demonstrated. There was a complete absence of the vagina. No estrin or prolan could be demonstrated in the urine by the Frank technic. The basal metabolic rate was -16 and -17 per cent on two consecutive tests. The patient weighed 164 pounds (74.4 kg.). A diagnosis was made of congenital absence of the vagina and hypothyroidism with endocrine dysfunction. On May 28, reconstruction of the vagina was carried out, utilizing an inlying split Thiersch graft after the method described. Fourteen days later the rubber tube was removed and replaced by a bakelite sound. The vagina was completely epithelized. Examination on Dec. 5, 1937, revealed a normal appearing vagina.

CASE 4.—An unmarried woman, 26 years of age, registered at the clinic on July 30, 1937, stating that she had never menstruated and had had no signs corresponding to those associated with menstruation. Her appetite was good. She had lost 30 pounds (13.6 kg.) in the past two years which she attributed to dieting.

On general physical examination the patient was found to have a normal feminine habitus and well-developed breasts. The labia were somewhat hypertrophied and the vagina was represented by a small indentation. The uterus could not be palpated on rectal examination, but a normal-sized ovary could be felt on the right side. The urinary estrin was positive (33 rat units for twenty-four hours). A diagnosis was made of congenital absence of the vagina. On August 10, reconstruction of the vagina was carried out, utilizing an inlying split Thiersch graft. Fifteen days later the tube was replaced by a bakelite vaginal dilator to be left in position for six months. The vagina was completely epithelized.

CASE 5.—An unmarried girl, 17 years of age, registered at the clinic on Nov. 15, 1937, stating that she had never menstruated, but had had sacral backache and some low abdominal pain associated with nausea and vomiting each month. Her general health had been good.

On physical examination she appeared to have a normal feminine habitus with well-developed breasts. Her weight was 128 pounds (58.1 kg.). On rectal examination she was found to have no vagina. Both ovaries could be palpated, although they were smaller than normal. While a cervix or uterus could not be palpated, a shelf or broad band could be felt in the position of the uterus. No urinary estrin could be demonstrated. A diagnosis was made of congenital absence of the vagina. Reconstruction was carried out on November 16, according to the technic described. Ten days later the tube was removed and replaced by a bakelite sound which was to be worn for six months. The vagina was completely epithelized with the exception of a small area in the vault.

CASE 6.—A married woman, 20 years of age, registered at the clinic on June 4, 1936. Two months prior to registration she had undergone instrumental delivery of a large baby. She was in labor twelve hours, a face presentation necessitating craniotomy. The patient's convalescence had been rather stormy and there was considerable fever. Fourteen days after delivery urine began to leak through the vagina.

performed it in one of his cases of stricture. In both of my cases of stricture the patients are menstruating, and in one I have some further plastic work to do on the cervix. When the cervix can be located, it is pulled into the rubber tube over which the graft is placed. This can only be done over a flexible rubber tube, as I have suggested. The grafts then grow over the anterior and posterior vault leaving the cervix exposed. If the cervix cannot be definitely exposed, then the end of the tube should be placed in the region of the cervical os, and it should not be covered by the skin graft. Later, blood may be seen making its appearance from a small aperture in the vault, and the cervical canal can then be definitely located and dilated. Stricture of the canal, if present, is handled by repeated dilatations.

SUMMARY

A brief review of the operative procedures for the correction of congenital absence or traumatic stricture of the vagina is presented. Some of the disadvantages associated with pedicle grafts and the risk involved in using any part of the intestinal tract are stressed. The McIndoe procedure is the operation of choice by reason of its simplicity and practicability. I have added certain modifications to this procedure which seem to me to be sound and useful.

Five patients with congenital absence of the vagina and two with traumatic stricture of the vagina were treated successfully and without mortality by this method.

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Leucoplakia, kraurosis, neurotic pruritus and atrophic vulvitis are various names given to conditions which are the results of the same deficiency. According to Swift, this deficiency is due to a lack of absorption of vitamin A, caused by a varying degree of achlorhydria. He observed a series of women with intractable pruritus associated with achlorhydria and other signs of a deficiency of vitamin A. The addition of dilute hydrochloric acid to the normal diet (one teaspoonful in a glass of water) relieves as a rule the pruritus and other vulvar affections. Half of this solution is to be sipped during and the other half drunk after each meal.

Vitamin A in the form of cod liver oil should also be given. It is suggested that excision of the vulva is not necessary except in cases in which there is suspicion of a malignant change. Epithelioma of the vulva should become increasingly rarer if this chronic irritation is relieved at any early stage. Achlorhydria is often present in cases of pruritus vulvae in which the irritation has not been relieved by treating the supposed primary cause.

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was incised, gradually separating the bladder and rectum, which were completely adherent. The reflection of the peritoneum was observed. There was no evidence of vaginal epithelium anywhere, so that a completely new vagina was made by an inlying graft after the method described. The cervix could not be identified. Eleven days later the tube was removed and the tract was almost completely epithelized. A bakelite vaginal sound was placed in position; this was to be worn for six months. Six weeks later examination of the vagina showed it to be of normal depth and diameter and to be completely epithelized except around the region of the cervix. The patient had by then had one menstrual period, and on examination I could visualize blood oozing through one spot in the vault of the vagina which probably represents the cervix. This is to be dilated and reconstructed at a later date.

COMMENT

I rather suspect that the incidence of congenital absence of the vagina is much greater than was formerly believed because there must be some who fail to seek treatment and the cases of many who do seek treatment are not reported in the literature. Some who do seek treatment refuse the abdominal operation because of its magnitude, and some, even though they are most anxious to have the defect corrected, hesitate to submit to the multiple stage procedure with the repeated trips to the hospital which are necessary when pedicle grafts are used.

Simplicity in surgery leads to more successes than do complicated operations; the mortality rate drops and the field of applicability becomes greater to more surgeons, so that the patients always benefit by it. I believe it can safely be stated that patients with congenital absence or atresia of the vagina no longer need fear the operation necessary to correct it. The procedure can be carried out by any surgeon familiar with skin grafting.

McIndoe has contributed enormously to the success of this operation by determining the period of contraction which is common to most cases in which an epithelized canal is constructed. If this period of contraction is disregarded, the operation becomes a failure. The contraction phase is, I believe, longer in cases of traumatic stricture than in those of congenital absence, since in the former, one is dealing primarily with a field of scar tissue. I have recommended, therefore, that the dilator be kept in position nine months instead of six months.

Patients are almost always interested in the degree of scarring on the thigh from removal of the graft. If the graft is accurately cut as a Thiersch graft, there is practically no scar at all, but if the full thickness of the skin is inadvertently taken, a scar will result. When it does develop, radium therapy has accomplished much in eradicating the scar tissue.

The surgical management of stricture is much more difficult than that of congenital absence of the vagina. Extreme care must be exercised to avoid injury to the urethra, bladder, and rectum, since it is necessary to form the new vaginal tract by sharp dissection through the dense, and too often inflamed, scar tissue. Also, fistulas to the surrounding organs may have been previously closed, and recurrence of these can be avoided only by exercising extreme caution. The cervix should be located if possible so that the patient can again menstruate. If this is not practical, owing to extensive trauma, then hysterectomy is in order. Baldwin

it be so. The outcome is too uncertain for the fetus, and the jeopardy to the mother too great to permit it to be commonly accepted as a suitable indication for bag insertion.

Observations on the selection of the bag disclosed the following data. The No. 5 and No. 6 Voorhees' bag was used 241 times or 65 per cent of the total. The smaller bags, No. 2, No. 3 and No. 4, were used 131 times in all or 35 per cent. Disregarding the influence of other factors, this shows a marked tendency to utilize large bags when any are indicated, a tendency which is neither invariably safe nor wise. After considering all pertinent data No. 4 and No. 5 bags are believed to be the most valuable in common use.

TABLE I. INDICATIONS FOR 372 BAG INDUCTIONS IN 25,969 DELIVERIES—INCIDENCE 1.4 PER CENT

	CASES BAGGED	
	NO.	PER CENT
<i>Pregnancy Diseases:</i>		
1. Placenta previa	60	16.1
2. Pre-eclampsia	72	19.3
3. Eclampsia	6	1.6
4. Abruptio placentae	32	8.6
5. Primary uterine inertia	25	6.7
6. Intrauterine fetal death	16	4.3
7. Cervical dystocia	4	1.1
8. Premature rupture of membranes	13	3.5
9. Malpresentation, 4 transverse, 1 face	6	1.6
10. Polyhydramnios	5	1.3
<i>Postmaturity</i>	31	8.3
<i>Contracted Pelvis</i>	9	2.4
<i>Intercurrent Diseases:</i>		
1. Nephritis	65	17.4
2. Heart disease	17	4.6
3. Syphilis	11	3.0
4. Hypertension	6	1.6
5. Pyelitis	3	0.8
<i>No Reason</i>	15	4.0
<i>Others:</i> Miscarriage (4), fetal monstrosity (2), diabetes (2), upper respiratory infection (2), ovarian tumor (2), breech, mole, pernicious vomiting, chorea gravidarum, syphilitic psychosis, tuberculosis.		

The patients were considered in five-year age-groups to determine the effect of age upon the hours in labor. Patients in the age-groups over thirty were as prompt in response to bag induction and expelled the bag within time limits as efficiently as the age-groups between 15 and 30. The age of the patient was no factor in anticipating the promptness of response nor the rapidity of labor.

There were 84 primiparas, comprising 22.6 per cent of the total; multiparas, 288 or 77.4 per cent. More than half of the multiparas were over thirty years of age. Only 17, or 20 per cent, of the primiparas were over 30 when induced by bagging.

The smaller bags were retained longer than the larger. The No. 3 bag was retained more than twelve hours in 37 per cent of the times used, the No. 4 bag, 20.6 per cent and the No. 5 bag, 20 per cent. The No. 6 bag in 33 per cent. There seems to be a tendency for labor to ensue earlier and progress more rapidly when No. 4 and No. 5 bags are used.

The cervix was soft and either partly effaced or dilated in most instances, although occasionally a large bag was inserted through a long undilated cervix. This is not good practice.

THE DILATING BAG IN OBSTETRICS*

ITS USE, ABUSE AND HAZARDS

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THE purpose of this paper is not to extol the virtues of one particular method of inducing labor, but rather comprehensively to consider the dilating bag, that it may be judiciously employed with the operator fully cognizant of its insufficiencies and the accidents attending its use.

Cesarean section unquestionably is not the answer to all obstetric difficulties, nor the routine method for terminating labor. Medical induction of labor is successful in a sufficient majority of instances to warrant its trial when the need is evident. When medical induction fails, recourse must be made to mechanical means. The two common forms in present day use are (1) artificial rupture of membranes and (2) intrauterine insertion of the dilating bag. It is the second method with which we are concerned, and the bag used is the Voorhees' modification of the Champetier de Ribes'.

The use of the bag is neither recent nor new. An early form was devised by Braun in 1851 and Champetier de Ribes described his in 1888, giving considerable impetus to its use. Dangers and defects inherent in the mechanical construction of bags in use were not overcome until Voorhees modified the de Ribes' bag in 1897 and published in 1913 experiences in 634 inductions at Sloan Hospital for Women. Since then, the bag has had wide usage, judging from published reports, but there seems to be a marked recession in recent years, even at Sloan. Following a preliminary reading of our experiences two years ago, the incidence has diminished in our own experience. It is possible that some cogent reasons for this may be revealed in this study, which details pertinent data concerned with the use of the Voorhees' bag in obstetrics in 372 cases occurring in 25,969 parturitions at the Margaret Hague Maternity Hospital, an incidence of 1.4 per cent.

INDICATIONS

The conditions indicating the use of the bag are given with their frequency in Table I. It is observed that well-recognized indications, such as placenta previa, pre-eclampsic toxemia, abruptio placentae, primary uterine inertia, nephritis and heart disease, account for over 70 per cent of the total.

The soundness of bag induction in inevitable abortion, cervical dystocia, and hydatid mole is open to question. Postmaturity was a convenient indication in 31 or over 8 per cent of the entire group. It is only fair to state that nearly half of these were done "experimentally" during studies on intrauterine hydrostatics during labor pains. In older publications contracted pelvis occupied a prominent place as a cause for bag induction. This is not so in our experience nor should

*Read at a meeting of the New York Obstetrical Society, January 11, 1938.

Rupture of the bag occurred once from overexpansion, and leakage occurred three times, without resultant damage. The cervix was found to be injured in many cases where operative delivery followed bag induction, but severe cervical damage was noted in but 9 patients. The use of weights increased the incidence of cervical damage. Twice uterine tetany ensued when a large bag was inserted through a hard, closed cervix, the upper segment apparently became overactivated and over-irritated, with the lower failing to expand and retract.

TABLE II. RELATIONSHIP OF SIZE OF BAG AND PARITY TO COMPLICATIONS

BAG SIZE	TIMES USED	CORD PRO- LAPSE AFTER BAGGING	PROLAPSE OF ARM	DISPLACEMENT WITH CHANGE OF PRESENTATION	INFECTION DUE TO BAG (?)
2	9			1	
3	24			2	
4	98	6	1	7	4
5	201	20	5	20	9
6	40	3	1	4	1
Total	372	29 (8%)	7	34 (9%)	14
Primiparas	84	8	2	9	5
Multiparas	288	21	5	25	9

The danger to the mother's soft parts, especially cervix and perineum, is largely due to the 50 per cent incidence of operative termination of the second stage of labor which this series showed. Rupture of the uterus through use of a large bag was not encountered, but the danger is real, if bags are improperly used at the third or fourth month of pregnancy. This was done four times in this series, and represented inadequate appreciation of the purpose and use of the dilating bag. The likelihood of morbidity and the often serious problems aroused by the failure of the uterus to respond are substantial hazards. The bag failed 14 times, or 3.7 per cent, and six of these patients had cesarean sections. Such gross errors in judgment obviously increase maternal risk. Forty-six cases or 12.3 per cent were morbid. It is doubtful if this morbidity percentage can be materially lessened inasmuch as all of these bag inductions were performed under most rigid operating room aseptic technic. It is only fair to direct the attention to the fact shown in Table III that more than 25 per cent of these morbid cases were determined only by aberrations in temperature over the allotted 100.4° F. on two readings after the first day. Twelve patients in this group showed no clinical or laboratory signs indicating any sepsis either relating to the bag or to the patient systemically, but are nevertheless classified because of their temperature reading. Many of the other causes for morbidity, as noted in Table III, cannot be ascribed or connected to the use of the bag. There were 9 maternal deaths or 2.4 per cent, occurring within twelve days of delivery. With one exception, the cause of death was the indication for inducing labor. One severe chronic nephritic patient succumbed four hours after a second bag induction, after having unsuccessfully entertained the first for twenty-four hours.

TABLE III. MORBIDITY

Total of Morbid Cases	46 or 12.3%
<i>Causes of Morbidity:</i>	
1. Not determined	12
2. Endometritis, foul lochia	18
3. Intrauterine fetal death	5
4. Thrombophlebitis	2
5. Pyelonephritis	3
6. Carbuncle of thigh	1
7. Bronchial asthma	2
8. <i>B. coli</i> septicemia	1
9. Retained placenta	2

METHOD OF INTRODUCTION AND USE OF WEIGHTS

While it was impossible to keep accurate data relating to intra- or extraovular bag emplacement, it was recorded that the membranes were artificially ruptured in the first stage in over 50 per cent of the cases. The recommended procedure was extraovular insertion except for placenta previa, but frequently the membranes were accidentally or deliberately ruptured, doubtless partly accounting for some of the 32 cases of prolapsed cords. The wisdom of rupturing the membranes purposely in conditions other than placenta previa or abruption of the placenta is questioned.

The use of weights was considered and the effects noted. They were found to be useless as accelerators of labor, and of no value except under two conditions: in assisting placental tamponade in placenta previa, and in keeping a small cervix filled where an oversize bag had been introduced. Then 1½ or 2 pound weights were employed over a properly adjusted pulley. The use of weights always increased the patient's discomfort considerably and increased the frequency of cervical lacerations. They tended to drag the dilator through an unprepared cervix which failed to efface and retract as it dilated and frequently closed down as soon as the bag was expelled.

ANESTHESIA

Operative delivery followed bag induction in nearly 50 per cent of the 372 cases. This meant double anesthesia danger, if anesthesia were used for the introduction of the bag. It was found that those with *most experience* in bag introduction used anesthesia with the *least frequency*. The only condition which required its use with seeming unanimity was the seldom justified insertion through a long hard or undilated cervix. Comprehensive knowledge of technic of introduction coupled with gentleness and sympathetic assurance adequately supplant the anesthetist.

OBSERVATIONS AFTER INSERTION

After insertion, labor contractions were initiated in 55 per cent of the cases within one hour, and lasted an average of 10.4 hours in all cases. Where the bag was expelled within 12 hours, the average was 5.7 hours; within 18 hours, 7 hours; and within 24 hours, 7.8 hours. The likelihood of failure materially increases after the 12-hour period has passed, the gross 4.5 per cent rising to 20 per cent of failures in patients laboring beyond 12 hours. This fact acquires greater significance when it is recalled that the morbidity rate in patients requiring operative termination of labor increases rapidly after the first 12 hours of labor have passed.

Oxytocics were used in but few cases, pitocin being employed in 3 minim doses. Latterly, pitocin was given in 3 minim doses at half-hour intervals to maintain or restore contractions after expulsion of the bag. The drug is always given hypodermically and never in excess of 3 minim doses, the hypodermic use being selected over other methods of introduction in the belief that a definite measured dosage of known absorption is preferable to other routes where the degree of absorption leaves the operator in some uncertainty as to the exact amount that was absorbed. The circumspect use of this drug was of definite value where failure might otherwise have been expected.

The bag advance was checked and the bag deflated and removed after expulsion through the cervix. In the first 244 cases of bag induction, vaginal examinations were made upon only 20 per cent of patients after bag expulsion. The revelation that this omission in technic cost the lives of several babies is of sufficient merit to justify this entire study.

COMPLICATIONS

Hazards were noted with respect (1) to those inherent in the bag, (2) to the patient, and (3) to the fetus.

TABLE VII. FETAL DEATHS

	NO.	PER CENT
Prior to bagging	57	15.3
Following bag induction	64	17.2
Total	121	32.5
Monstrosities, nonviable prematures and fetal deaths prior to bagging	92	
Corrected fetal deaths	29	7.8

CAUSES		CAUSES	
1. Prematurity		2. Abruptio placentae	22
Under 7 mo.	27	3. Placenta previa	16
7-8 mo.	26	4. Toxemia pregnancy	31
8-8½ mo.	15	5. Chronic nephritis	17
All under 2500 gm.		6. Syphilis	3
2. Neonatal		7. Malfetation	2
First day	8		
Second day	3		
Third day	4		

COMMENT

Clinical interpretation of the foregoing data has served to clarify and compose our position with respect to Voorhees' bag induction of labor. It is too valuable to be either disregarded or misused. The purpose of a bag is either to stimulate the uterus to contraction through irritation of the lower uterine segment, and effect cervical dilatation and effacement, or to cause these plus tamponade to check hemorrhage in placenta previa. It may occasionally be used to retain a replaced prolapsed cord. It is most useful at term, with the cervix softened and partly effaced and least valuable earlier in pregnancy when the cervix is long and tight. The bag must fit the cervix, and while small bags are attended by a greater likelihood of long labor or failure, there is less risk of prolapsed cord or displacement of presenting part. If the membranes are intact, it must always be placed extraovularly, except in placenta previa. With the exception of placenta previa, the size of the bag chosen depends upon the indication, the part presenting and the condition of the cervix, although No. 4 and No. 5 give the best results in general. No traction is used except in placenta previa, unless the bag tends to slip upward. The bag must be filled until the stem is tense, for if partly filled it will slip into the vagina. In placenta previa, the largest bags that can be safely introduced are ones that most effectively tampon the bleeding area.

Since labor ensues early and with stronger pains than usual, the progress of the bag must be checked constantly by rectal examinations, and abdominal examinations made for change in uterine tension and fetal position. As soon as the bag is through the cervix, its function is completed and it is removed. A vaginal examination must be made immediately to look for prolapse of cord and malpresentation, the two most frequent causes of stillbirths. Either complication compels prompt delivery if the cervix is completely effaced and dilated or easily dilatable. Hemorrhage from placenta previa after bag expulsion likewise forces prompt action, and version-tamponade is the usual procedure of election.

Other management might have temporarily spared this patient, and possibly two others with abruption of the placenta.

The baby's life was imperiled by many contingencies. The cord prolapsed in 32 cases, with a loss of 23 babies, 18 after bag induction. Of 121 fetal deaths, 64, or 53 per cent, *followed* induction of labor with the Voorhees' bag. Excluding nonviable prematures, miscarriages, monstrosities, and those dead before introduction of the bag, there were 29 fetal deaths, or 7.7 per cent, an appreciable number.

The fetal position changed in 34 patients after bagging, an incidence of 9 per cent, and the fetus succumbed in 9 of these. Only thrice was the change of position more favorable for delivery.

TABLE IV. COMPLICATIONS 372 BAG INDUCTIONS

COMPLICATION	BEFORE BAGGING	AFTER BAGGING	TOTAL	FETAL DEATHS		TOTAL
				BEFORE BAGGING	AFTER BAGGING	
Prolapsed cord	3	29	32	5	18	23
Change of presentation		34	34	1	8	9
Pelvic infection		14	14	1	3	4
Hemorrhage	11	2	13	4		4
Prolapsed arm	3	4	7	3		3
Retained placenta		5	5	2	1	3
Shock	1	3	4		1	1
Secondary anemia	3	20	23		2	2
Lacerations, 2°		18	18		1	1
Lacerations, 3°		3	3			

Twin pregnancy (3), deep cervical laceration (2), thrombophlebitis of legs (2), bronchopneumonia, breast abscess, asthma, vulvar infection, furuncle of thigh, rectovaginal fistula (old), acute nephritis.

TABLE V. OPERATIVE INTERFERENCE

1. Forceps:	
Low	31
Mid	15
2. Version and extraction	92
3. Breech extraction	28
4. Cesarean section	6
5. Craniotomy	5
6. Manual removal of placenta	2
7. Vaginal cesarean section	1

180—48.4 per cent

Membranes artificially ruptured in over 50 per cent of cases in first stage of labor, not good practice!

TABLE VI. MORTALITY

CASE	MORTALITY	DEATH FOLLOWED IN
102	Eclampsia	24 hours
769	Cerebrospinal syphilis	5 days
1,488	Chronic nephritis, cerebral apoplexy	12 hours
13,166	Chronic nephritis, chronic cardiac disease	8 days
1,418	Chronic nephritis, 2 baggings	4 hours
11,496	Chronic nephritis, abruptio placentae	7 hours
7,276	Abruptio placentae, placenta previa	24 hours
14,966	Uteroplacental apoplexy	6 hours
1,013	Uteroplacental apoplexy	10 hours
Total—9 deaths—2.4 per cent.		

and, in the hands of properly trained obstetricians, will give as good results in the immediate pregnancy, and safer deliveries in subsequent pregnancies, than cesarean sections which are now so popular for this condition.

Another use of the bag is in cases where it is impossible to get either the ovum or presenting part well down into the lower uterine segment. It is essential to have something in the lower uterine segment and cervix in order to have adequate labor.

I would criticize the size of the bags which Dr. Waters advocates. Except in some serious cases of placenta previa, a No. 5 bag is seldom indicated. Again, the attachment of weights to the stem, $1\frac{1}{2}$ to 2 pounds or more, causes spasmodic contractions of the uterus, pulls the bag through the cervix, and seldom induces labor properly.

DR. GEORGE H. RYDER.—The dilating bag was used too frequently twenty years ago, and for that reason it fell into disfavor with many obstetricians. Its main uses then were for the induction of labor and for stimulating labor already begun. In both of these indications, pituitrin can now usually be used instead.

There are still, however, certain conditions where the bag can be used to advantage, namely dry labors with rigid cervixes, where pituitrin or thymophysin have been unsatisfactory, and in breech presentations.

In a series of 1,400 consecutive deliveries in private practice I have used the bag 67 times, with a corrected morbidity of 4.47 per cent, and no maternal mortality from puerperal infection. There were two prolapsed cords, in the 67, with one fetal death. No change of presentation or position of the fetus occurred. These two complications result from using a bag too large for the dilatation of the cervix.

DR. SAMUEL A. COSGROVE.—The largest bag that can be introduced through the cervical dilatation present is the best one. My own preference is a No. 4 bag, which can be introduced through a cervix dilatation of one finger. Then the action of the bag is as prompt and certain as it is possible to be. Inasmuch as many of the indications for which the bag is employed themselves jeopardize the child, it is not unreasonable to accept a certain fetal loss, dependent on the inevitable occasional prolapse of the cord and disturbance of position, which I admit the use of those large bags entails. On the other hand if a succession of small bags is used, the infective risk to the mother is definitely increased. As to weighting the bags, I believe that a small weight applied to the tube when a large bag is used is useful to keep the bag in the axis of the vagina, thus permitting it to act efficiently as the uterus contracts behind it.

I would emphasize most strongly what Dr. Waters has said about the necessity of following the bag carefully once it is introduced, and removing it as soon as it has performed its function, in order that any possible complication following its use may be recognized and dealt with.

DR. HARVEY B. MATTHEWS.—I have never put a weight on a bag in the cervix, but I have seen at least two very sad accidents from deep lacerations through the cervix and the lower uterine segment following the use of weights. To advise the general use of a weight attached to a bag in the cervix is certainly not desirable.

In the hands of the expert who knows the size of the pelvis and appreciates the approximate size of the postmature infant, induction might be practiced. I personally would rather let the patient go ahead until labor begins, give her a fair test of labor and accomplish delivery by the use of whatever method seemed indicated at the time.

In regard to the size of the bag, I rarely use one larger than No. 4, very, very occasionally perhaps a No. 5. I have never used a No. 6.

Infection need not necessarily be a hazard in using bags. We have very little if any more morbidity in our bag cases with the use of mercurochrome and hence do not fear infection.

If the uterine contractions cease with the expulsion of the bag, hypodermic pitocin in one to three minim doses at half hour intervals is indicated; none are given after resumption of pains, and larger doses are absolutely prohibited. If conditions are favorable, expectant observation should take precedence over operative manipulations, with their high morbidity and fetal mortality.

CONCLUSIONS

1. Experiences accompanying the use of the Voorhees' dilating bag in 25,969 deliveries with an incidence of 1.4 per cent are recounted.

2. Bag induction of labor is a valuable adjunct to manipulative obstetric practice, with clear-cut indications which one cannot refute.

3. The factors of pregnancy duration, parity, size of bag, insertion with respect to membranes, and use of weights have a direct bearing upon the events subsequent to bag insertion.

4. A proper technic permits introduction without anesthesia, an important actuality in view of imperative anesthesia accompanying the nearly 50 per cent operative incidence subsequent to bagging.

5. The outstanding fetal hazards are prolapse of cord and production of malpresentation, with high fetal death rate.

6. Those who use the dilating bag should be aware of its proper indications and its hazards and know and practice proper technic in its application.

I wish to express my very sincere thanks to Dr. James W. Ravenscroft, Medical-Dental Building, San Diego, California, and Dr. Elbridge E. Anderson, 234 Doctors' Building, Nashville, Tennessee, who materially assisted in the compilation of data used in an unpublished paper covering 12,000 deliveries, which forms part of the present publication.

DISCUSSION

DR. WILLIAM E. CALDWELL.—Gradually, induction of labor with the Voorhees' bag has become unpopular. Other methods have been developed, chiefly the use of pituitrin and the early rupture of the membranes. I fear that these also complicate what should be a normal labor, unless the doctor has excellent judgment as to the time of induction and skill enough to get out of trouble when it occurs. Induction of labor to get a small, premature baby through a small pelvis is seldom advised. The number of labors induced for this reason which have been unsatisfactory, the large percentage of operative deliveries, and the well-recognized truth that a premature baby does not stand a difficult labor or operative procedure well, have led to leaving the woman alone until she goes into labor. Then, if necessary, the delivery may be terminated by a low-flap cesarean section or extraperitoneal operation.

The fear of postmature babies, which was a common indication for induction of labor, has been decreased by the knowledge that very few babies actually are postmature. Complications endangering the life of mother or child are well handled with induction of labor if the lower uterine segment has been formed and a soft, and a dilatable cervix is present.

The chief function of the bag at the present time is to control bleeding in placenta previa. There is no question that the bag works well in controlling hemorrhage and the chief cause of trouble in this method is the need for an immediate delivery after the bag comes through a cervix which is not always completely dilated or retracted. Further labor, or cutting the anterior lip of the cervix, is feasible

A TEN-YEAR STUDY OF CESAREAN SECTION IN THE ST. LOUIS MATERNITY HOSPITAL

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IN 1933 a study of maternal deaths, in fifteen states which were included in the birth registration area, was made by the obstetric advisory committee of the United States Children's Bureau.¹ Regarding deaths following cesarean section it was commented. . . . "that there had been unwise selection of cases for operation, or of the types of operation, or both. . . ." In 1935, Stander² presenting statistics from the Woman's Clinic of the New York Hospital felt "the need to place this life-saving operation in its proper setting, both in regard to the indications and in respect to time and skill of operation, in order that its abuse may become legendary and the maternal mortality rate may be held within narrow minimal limits."

Numerous reports in the recent literature from private and teaching centers indicate a steadily increasing incidence of cesarean sections and a progressive decrease in maternal mortality.

This study encompasses the ten-year period from the opening of the St. Louis Maternity Hospital on Aug. 15, 1927 to Aug. 15, 1937. During this time there has been a change in incidence of operation, indications, type of operation, maternal mortality and maternal morbidity. Tables I to IX depict the experiences and results. The information has been analyzed in aggregate, in five-year periods and from the point of view of ward and private services.

INCIDENCE

Among 17,170 hospital deliveries during the ten-year period, 304 cesarean sections were performed (Table I).

Of these, 43 per cent were performed during the first five years and 57 per cent during the second period; this in spite of the fact that 56.2 per cent of all hospital deliveries occurred during the first five years.

The increase in frequency of operation from one in 88.5 to one in 51.5 deliveries on the ward service, and from one in 54.9 to one in 34.6 on the private service is significant. For the combined service, the recent incidence of 2.3 per cent, or one in 43.4 cases, indicates the progressive frequency with which cesarean section is being performed. Study of subsequent charts will explain the increase in incidence of operation.

Of the operations 55.2 per cent were primary and 44.8 per cent were repeat operations. The incidence of secondary operations was approximately the same on both ward and private cases.

I have only two or three indications for the use of bags. Most important of these is induction in the presence of a severe toxemia and in placenta previa, where cesarean section is not indicated.

Whether you should introduce a bag intraovularly or extraovularly does not make any difference as far as the efficacy of the bag is concerned. Personally I like to keep the membranes intact because there is always a rim of cervix remaining after the bag is expelled and the "forewaters" are helpful in obtaining full dilatation and delivery without undue laceration.

DR. ARTHUR W. BINGHAM.—There are two reasons for the bag falling into disrepute. One is that the indications have increased entirely too much and the other that the size of the bag has increased too much. I never use a bag larger than a No. 3 except occasionally in marginal placenta previa, where I have used a No. 4. I never knew there was a No. 6 until the other day in investigating a death in New Jersey, I found a No. 6 bag had been used and a laceration of the cervix had resulted.

DR. WATERS (closing).—Since presenting a similar analysis in 10,000 cases two and a half years ago, our use of the bag has dropped considerably because of our more rigid adherence to proper indications. More than 70 per cent of all indications are for placenta previa, preeclampsia without pelvic disproportion, abruption of the placenta where vaginal delivery seems preferable to the abdominal route, primary inertia of the uterus and intrauterine fetal death. Of the 31 cases done for postmaturity, more than half were done in conjunction with a study being carried on. In contracted pelvis the bag was used an inconsiderable number of times. Obviously this is contraindicated except with a very small fetus.

Judging from our experience and from all the criteria available in this study, the No. 4 and No. 5 bags are the preferable sizes for the majority of cases. I still believe weights are valueless with rare exceptions, and are much more likely to do harm than to be of good. Most of the women in this series who had severe lacerations of the cervix were those who had weights used. They also increased the pain of lower segment distention, adding further to the patient's discomfort.

Reference to the morbidity table will show that approximately 25 per cent of our morbidities had no basis in the patient's course other than in her temperature readings and that a good many causes of fever, such as carbuncle of the thigh, bronchial asthma, etc., certainly could not be ascribed to bag induction. If we were to limit morbidity ascribable to the bag to cases showing endometrial or pelvic infection, the morbidity would be lowered to approximately 5 per cent.

Reifferscheid, W.: Local Treatment of Pruritus Vulvae With Follicle Hormone, *Monatschr. f. Geburtsh. u. Gynäk.* 106: 287, 1937.

During 1924-1935 twenty-six patients with kraurosis vulvae were treated by means of radiation in the Würzburg clinic. Only one-third of these women were relieved. A noteworthy advance in the treatment of kraurosis was first suggested by Buschbeck and Seitz, namely, the use of follicle hormone. Subcutaneous injections yielded good results but Reifferscheid decided to apply follicle hormone locally in the form of a salve. This form of therapy proved to be most helpful and the author recommends its use for all cases of kraurosis vulvae. Even if it does not produce a cure it will result in great relief and improvement when used together with hypodermic injections.

J. P. GREENHILL.

operation. The medical condition is considered to be the fundamental indication for operation with the sterilization indication induced by the underlying medical state. It is this change in indication which is chiefly responsible for the increase in incidence of cesarean operations on the ward service.

TOXEMIA OF PREGNANCY

Toxemia of pregnancy is noted to be apparently less frequent as an indication for operation on both ward and private services in the latter five-year period. Of 24 ward sections, 10 were performed for eclampsia, 7 were for severe pre-eclampsia, and 7 for chronic nephritis. The pre-eclamptic patients were operated upon, with the toxemia as the only indication. In other cases a milder state of toxemia existed but the associated conditions such as large baby with danger of prolonged labor, desire for sterilization and tumors of the uterus were the primary indications for operation.

The apparently greater frequency of toxemia on ward than on private service warrants consideration. Although toxemias of pregnancy are noted more often on the wards, many of the severe cases are sent to the ward service by outside physicians, so that their consideration as ward patients is really not a true status.

Study of all toxemia patients in both periods indicates that approximately one-third fewer toxemia patients were observed during the latter five-year period. Thus one-half as many operations were performed on approximately two-thirds as many patients, less of a reduction in percentage incidence than study of Table II indicates.

TABLE II. INDICATIONS

	1927-1932		1932-1937		TOTAL 1927-1937	
	NO. CASES	%	NO. CASES	%	NO. CASES	%
<i>Private</i>						
Contracted pelvis	14	24.1	24	28.9	38	26.9
Tumors	6	10.4	9	10.8	15	10.6
Medical indications	5	8.6	7	8.4	12	8.5
Postmaturity	4	6.9	8	9.6	12	8.5
Placenta previa	5	8.6	6	7.3	11	7.8
Toxemias	6	10.4	3	3.6	9	6.4
Previous section	4	6.9	4	4.8	8	5.7
Cervical dystocia	1	1.7	6	7.3	7	4.9
Previous plastic	4	6.9	2	2.4	6	4.2
Miscellaneous	9	15.6	14	16.8	23	16.4
<i>Ward</i>						
Contracted pelvis	33	45.2	33	36.6	66	40.5
Medical indications	5	6.8	38	42.2	43	26.4
Toxemias	16	21.9	8	8.9	24	14.8
Tumors	5	6.8	3	3.4	8	5.0
Postmaturity	4	5.5	1	1.1	5	3.1
Cervical dystocia	1	1.4	3	3.4	4	2.5
Placenta previa	2	2.8	1	1.1	3	1.3
Miscellaneous	7	9.6	3	3.3	10	6.3

PLACENTA PREVIA

Eleven private patients were operated because of placenta previa and only three on the ward service.

In previous years a difference in handling such cases existed on the two services. In addition to blood transfusions and general supportive measures, the ward cases were treated formerly by packing properly inserted. More recently partial and central placenta previa with viable babies are treated by cesarean section.

The incidence of all placenta previa cases is the same among ward and private cases. A study of these cases is now in progress.

TABLE I. INCIDENCE

	WARD	PRIVATE	COMBINED
1927-1932:			
Number of deliveries	6,466	3,189	9,655
Number of sections	73	58	131
Frequency	{ 1.12% 1-88.5	1.81% 1-54.9	1.35% 1-73.7
1932-1937:			
Number of deliveries	4,635	2,880	7,515
Number of sections	90	83	173
Frequency	{ 1.93% 1-51.5	2.88% 1-34.6	2.30% 1-43.4
1927-1937:			
Number of deliveries	11,101	6,069	17,170
Number of sections	163	141	304
Frequency	{ 1.46% 1-68.1	2.32% 1-43.0	1.77% 1-56.4

PARITY

Among the ward patients, during the first five years, 45 per cent of the patients operated upon were primiparas, and 38 per cent had had one or two previous pregnancies, a total of 83 per cent being para iii or less at the time of operation. Consistent with the increase in medical indication for operation and the high incidence of sterilization, we find that during the second five years, 24.7 per cent were primiparas and 28 per cent had one or two previous pregnancies, a total of 52.7 per cent gravida iii or less, and 47.3 per cent multiparas greater than iii at the time operated.

On the private service, during the first five years, 53.4 per cent of operations were performed in primiparas and 86.2 per cent on para iii or less. During the recent five-year period, again consistent with essentially the same general indications as previously, 61.7 per cent of the operations were performed on primiparas and 93.8 per cent on para iii or less at the time of operation.

INDICATIONS

Indications for cesarean section have been classified by ward and private services in each of the two five-year periods.

Apart from contracted pelvis as an indication the private and ward services differ greatly. On the private service is noted a greater diversity of percentage indication. An attempt is made, in this study, to list only the primary indications for operation. The difficulties offered in such a classification were more pronounced on the private service. Essentially, the indications for operation on private cases is the same in each five year group. The increase in frequency of operation cannot be attributed to a change in indications.

CONTRACTED PELVIS

Contracted pelvis is the most frequent indication for operation on both services, accounting for 40.5 per cent of all ward and 26.9 per cent of private operations, a combined incidence of 34.2 per cent.

MEDICAL INDICATIONS

During the first five years, 6.8 per cent of all ward operations were performed for medical reasons; during the second period 42.2 per cent were operated for similar reasons. This group of patients included cardiac, pulmonary and thyroid disease, essential hypertension, arthritis, patients with marked varicose veins, psychiatric and neurologic conditions. All of these patients were sterilized at the time of

MATERNAL MORTALITY

Table III shows the maternal mortality during the two five-year periods. Only one maternal death occurred in 173 operations performed during the past five years. The factors to be considered in this lowered mortality rate include the increase in number of elective operations, preparation of the patient for operation with antiseptic vaginal instillations and possibly the choice of type of operation.

TABLE III. MATERNAL MORTALITY

(Combined Service)

5-YEAR PERIODS	DEATHS	OPERATIONS	MORTALITY PER CENT
Aug. 15, 1927 to Aug. 15, 1932	8	131	6.10
Aug. 15, 1932 to Aug. 15, 1937	1	173	0.57
Total	9	304	2.96

Table IV presents a protocol of the maternal deaths. Seven deaths occurred in elective cases and 2 after the onset of labor. Four of the 9 deaths (44 per cent) were attributable to sepsis. Two deaths in 1929 occurred during a mild epidemic of staphylococcus infections.

TABLE IV. MATERNAL DEATHS; 1927-1937

1. 4668. Ward. Previous section. Flat rachitic pelvis. Elective. Low cervical. Pneumonia.
2. 12940. Ward. Flat rachitic pelvis. Long labor on outside. Low cervical. Septicemia.
3. 13492. Ward. Eclampsia without coma or convulsions. Elective. Classical.
4. 13450. Private. Decompensated cardiac. Elective. Classical.
5. 5915. Private. Inertia. Ruptured membranes 3 days. Classical. <i>Staphylococcus albus</i> peritonitis.
6. 9155. Ward. Contracted pelvis. Eclampsia. Elective. Low cervical. Adynamic ileus.
7. 2049. Ward. Incarcerated myoma. Elective. Porro. Hemorrhage from pedicle.
8. 6148. Private. Toxemia. Elective. Low cervical. <i>Staphylococcus albus</i> .
9. 18722. Ward. Nephritis. Heart disease. Elective. Low cervical + hysterectomy. 4 hour postoperative shock. Cardiac.

The deaths with relation to the indication for operation are reviewed in Table V.

Table VI demonstrates that there has been no maternal death with the performance of the transverse low cervical operation. Explanation of the high mortality with the longitudinal low cervical operation lies in Table IV.

The maternal mortality for the entire series is 2.96 per cent. The mortality for the last five years is 0.57 per cent.

DURATION OF LABOR

On the ward service during the first five years, 60.5 per cent of cesarean sections were performed as elective operations with no labor, 18.3 per cent in labor 0 to 12 hours, 11.2 per cent in labor 12 to 24 hours, and 10 per cent in labor more than 24 hours. During the second period of time, 82 per cent of the ward operations were elective, 10 per cent in labor 0 to 12 hours, 4.5 per cent in labor 12 to 24 hours, and 3.5 per cent in labor more than 24 hours. More frequently, recently, possible cesarean section patients are hospitalized, prepared, and operated upon sooner than formerly.

The average weight of babies of ward placenta previa cases is 2,550 gm. as compared with 3,240 gm. on the private service. This would indicate that the private patient on the average carries her baby nearer to term.

With cesarean section reserved for those cases where there is reasonable expectancy of obtaining a good living baby, the explanation of the greater number of private patients sectioned for placenta previa is obtained.

TUMORS

Seven of 8 ward patients operated upon for tumors were treated by hysterectomy. One tumor was an impacted ovarian cyst.

Eight of 15 private patients were sterilized, the remaining patients treated by myomectomy following cesarean section.

POSTMATURITY

Among the ward cases these babies weighed between 4,000 and 5,100 gm. In every case, also, another indication for operation existed, mild pre-eclampsia, borderline pelvis or breech presentation.

On the private service the greater frequency of this indication is noted. Five of 12 operations were performed with postmaturity as the only indication. Such babies weighed between 3,800 and 6,200 gm. Three were performed on elderly primiparas with myomatous uteri or contracted pelvis. One each was associated with inertia, contracted pelvis, breech, and heart disease.

MISCELLANEOUS INDICATIONS

These indications included antepartum hemorrhage, contraction ring, elderly primiparas with breech, elderly primiparas with no complications, abruptio placentae, previous section with morbidity, previous section with peritonitis, previous section with breech, dwarfism, marked vaginal condylomas, aneurysm, marked umbilical hernia, and breech with fetal embarrassment.

TYPE OF OPERATION

Prior to 1927, practically all operations were of the classical type. From 1927 to 1932 the low cervical operation with longitudinal incision in the lower uterine segment was favored equally with the classical operation in the ward service. On the private service the classical operation was performed in 86.2 per cent of cases as compared with 13.8 per cent of the low cervical type; with a combined incidence of classical operation in 64.9 per cent of cases.

Since 1932, the low cervical operation with a transverse incision in the lower uterine segment, as advocated by Phaneuf,³ has become popular. On the private service the classical operation is still performed in 65 per cent of cases, but on the ward service 73.3 per cent of cases are of the low cervical type and 55.6 per cent of the ward operations are with the transverse incision in the lower segment.

The transverse low cervical operation is of especial value in those cases where hysterectomy is to be performed. The pedicles need but be clamped and cut to the level of the transverse incision, and the uterus is then removed readily by carrying the incision around posteriorly. The ease with which hysterectomy can be performed after the transverse low cervical incision is to be emphasized.

During the first five-year period, hysterectomy was performed after classical operation in 14 of 17 cases. During the second five-year period, 18 of 34 hysterectomies were performed after the transverse low cervical operation, 10 after classical and 5 after the longitudinal low cervical operations.

The longitudinal low cervical operation has never been very popular on the private service. During the ten-year period only 18 of 141 operations (12.7 per cent) on the private service were of the longitudinal low cervical type; whereas 19 transverse low flap operations (13.4 per cent) of the entire private service have been performed in the past four years alone.

TABLE VII. STERILIZATION

	1927-1932	1932-1937	TOTAL	PER CENT
<i>Private Patients</i>				
Number of sections	58	83	141	
Number of sterilizations	18	27	45	31.2
<i>Indications:</i>				
Contr. pelvis with previous section	5	3	8	
Contracted pelvis	1	1	2	
Tumors	3	5	8	
Previous plastic	3	2	5	
Medical indications	2	3	5	
Placenta previa	2	2	4	
Previous section	1	3	4	
Sterilization	0	3	3	
Cervical dystocia	0	2	2	
Toxemia	1	1	2	
Unclassified	0	2	2	
<i>Ward Patients</i>				
Number of sections	73	90	163	
Number of sterilizations	25	55	80	49.1
<i>Indications:</i>				
Medical indications	5	38	43	
Contr. pelvis with previous section	3	5	8	
Contracted pelvis	5	5	10	
Tumors	5	2	7	
Toxemia, nephritis	2	2	4	
Previous section	1	2	3	
Placenta previa	1	1	2	
Previous plastic	1	0	1	
Postmaturity with manipulation	1	0	1	
Stenosis cervix	1	0	1	

TABLE VIII. STERILIZATION: TYPE OF OPERATION

OPERATION	HYSTERECTOMY	TUBAL RESECTION
<i>Private Service</i>		
Classical	28	12
Longitudinal low cervical	1	0
Transverse low cervical	2	3
	31	15
<i>Ward Service</i>		
Classical	24	12
Longitudinal low cervical	9	3
Transverse low cervical	18	12
Unclassified	1	0
	52	27

FETAL MORTALITY

This is demonstrated in Table IX on ward and private services in each five-year period.

These statistics are not corrected for abnormality (hydrocephalus), prematurity, or operations performed solely in the interest of the mother without regard to the size of the baby. The explanation of the change in fetal mortality statistics is obtained by noting the indication for operation in the respective cases in which fetal mortality was observed.

Of the 11 fetal deaths in the first five-year period on the ward service, 5 were associated with long labors, 3, all prematures, were noted in nephritic toxemias, and

TABLE V. MATERNAL MORTALITY WITH RELATION TO INDICATION FOR OPERATION

INDICATION	NO. OF OPERATIONS	DEATHS	PER CENT MORTALITY
Contracted pelvis	104	3	2.88
Toxemia	33	2	6.06
Medical indications	55	2	3.63
Tumors	23	1	4.34
Miscellaneous		1	

TABLE VI. MATERNAL MORTALITY (10 YEARS)

TYPE OF OPERATION	WARD			PRIVATE			COMBINED		
	DEATHS	NO. OF OPERATIONS	MORT. %	DEATHS	NO. OF OPERATIONS	MORT. %	DEATHS	NO. OF OPERATIONS	MORT. %
Classical	2	58	3.44	2	104	1.92	4	162	2.46
Longitudinal	4	53	7.54	1	18	5.55	5	71	7.04
low cervical									
Transverse	0	51	0	0	19	0	0	70	0
low cervical									
Unclassified	0	1	0	0	0	0	0	1	0
Total	6	163	3.68	3	141	2.12	9	304	2.96

On the private service the duration of labor was essentially the same in each period. Eighty-two and four-tenths per cent were elective operations, 12.2 per cent were in labor 0 to 12 hours, and 5.2 per cent were in labor more than 12 hours.

PREPARATION OF PATIENT

The procedure of choice with patients who are to have elective cesarean sections or who are considered as possible candidates for this operation is as follows: The patients are hospitalized several days before contemplated operation and receive a complete medical work-up. Vaginal instillations of 8 c.c. of 1 per cent neutral acriflavine hydrochloride in glycerin are administered twice a day for a few days prior to operation. When in labor and the patient is being subjected to a test of labor such instillations are administered every eight hours.

As noted above in this discussion 92 per cent of the ward patients and 94.6 per cent of the private patients presented labors from 0 to not more than 12 hours. Table IV also demonstrates that 2 of the 9 deaths were associated with prolonged labor or long ruptured membranes.

It is felt, from the bacteriologic studies made from intrauterine cultures taken at the time of operation, that a definite safety measure exists in the use of the acriflavine instillations. More adequate tests of labor can be allowed under such procedure.

The bacteriologic studies performed in this series with analyses regarding duration of labor and maternal morbidity will be the subject of a separate communication by T. K. Brown of this department.

STERILIZATION

Table VII shows that 49.1 per cent of ward operations and 31.2 per cent of private cases were accompanied by a sterilization operation.

The high incidence of medical indications for operation here explains the major portion of the general increase in cesarean operations on the ward service during the period of time of this study.

Table VIII shows the various operations performed for sterilization purposes. Hysterectomy is the method of choice in this series, and in recent years performed most frequently after the transverse low cervical type of operation.

A COMPARISON OF THE END-RESULTS OF TREATMENT OF ENDOCERVICITIS BY ELECTROPHYSICAL METHODS: CAUTERY, COAGULATION, AND CONIZATION

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MANY therapeutic methods for chronic inflammation of the endocervix, including both chemical and physical agents, have been advocated and are in use at the present time. Those which utilize the electric cautery, the high frequency current adjusted to coagulate tissue, or the high frequency current regulated to excise portions of tissue, are probably the most popular. The technics for cautery,¹ coagulation,² and coning,³ of the cervix have been adequately described. Technically, the simplest of these procedures is coagulation, then cauterization, and the most difficult is conization, or coring of the cervical mucosa; however, all of these methods are easily carried out by the experienced gynecologist.

This investigation was undertaken to make a comparative estimate of the end-results in patients treated by these three methods. One hundred and fifty cases, 50 each treated with cautery, coagulation, and coning, were used in this study. Tables I to III indicate that the patients in every group presented similar symptoms and physical findings.

TABLE I. SOCIAL GROUP

	NUMBER OF CASES	AVERAGE AGE	M.	S.	CHILDREN		
					NONE	ONE	MORE
Cauterization	50	30	46	4	7	11	32
Coagulation	50	31	46	4	13	12	25
Conization	50	33	47	3	18	8	24

TABLE II. SYMPTOMS

	MENSTRUATION		DISCHARGE			PAIN		
	REG.	IRREG.	SLIGHT	MOD- ERATE	PRO- FUSE	NONE	BACK	LOWER QUAD.
Cauterization	40	10	22	11	17	14	19	23
Coagulation	37	13	17	10	23	15	21	21
Conization	42	8	16	11	23	15	19	19

TABLE III. PHYSICAL EXAMINATION

	EROSION			CYSTS			PARAMETRIUM	
	NONE	SLIGHT	MARKED	NONE	FEW	MANY	POST.	LATERAL
Cauterization	17	10	23	25	3	22	27	6
Coagulation	14	15	21	36	5	9	27	3
Conization	23	11	16	35	6	9	26	4

1 in an eclamptic mother. Thus 9 of the 11 deaths were associated with maternal conditions which today are modified indications for cesarean section.

TABLE IX. FETAL MORTALITY

	NO. DELIVERIES	NO. DEATHS	PER CENT
1927-1932:			
Private	58	4	6.9
Ward	73	11	15.0
Combined	131	15	11.4
1932-1937:			
Private	83	4	4.8
Ward	90	6	6.6
Combined	173	10	5.8

SUMMARY

1. The incidence of cesarean section has increased from 1:73.7 (1927-1932) to 1:43.4 (1932-1937).

2. The explanation of the increase in incidence on the ward service lies in the increase in number of operations performed for "medical" conditions rather than purely obstetric reasons.

3. The low segment operation is preferred on the ward service. In recent years the transverse incision in the lower segment has been the operation of choice.

4. The maternal mortality for ten years is 2.9 per cent. The maternal mortality for the past five years is 0.57 per cent.

5. Forty-four per cent of the maternal deaths were attributed to sepsis.

6. The use of one per cent acriflavine (neutral) hydrochloride in glycerin as a vaginal instillation before operation is recommended.

7. The uncorrected fetal mortality for ten years is 8.2 per cent; for the last five years, 5.8 per cent.

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Rodecurt: Late Results in Treatment of Pruritus Vulvae With Progynon, Zentralbl. f. Gynäk. 61: 2159, 1937.

In 1936 Rodecurt published his results in the treatment of pruritus vulvae by means of estrogenic substance. He concluded that the effects are too uncertain, that recurrences and bleeding are too frequent and difficult to avoid, to accept this expensive form of treatment as the method of choice. He now reconsiders this problem because he had occasion to reexamine four patients. All have been relieved of their disagreeable symptoms during the 12 to 22 months which have elapsed. Hence the author is now of the opinion that estrin therapy for pruritus vulvae is worth while.

J. P. GREENHILL.

dilatation promptly corrected the stenosis. In 4 patients following coagulation and in 3 after conization, a marked tuboovarian inflammation was excited. These patients were treated by rest in bed and given the usual treatment for acute pelvic inflammation. In 6 patients after coagulation of the cervix, a temporary amenorrhea followed, lasting from three to fourteen months. In one patient after coagulation and in one following conization, the next menstrual flow was unusually profuse.

TABLE VI. COMPLICATIONS

	CERVIX		INFLAMMATION TUBES AND OVARIES	MENSTRUATION	
	BLEEDING	STENOSIS		AMENOR- RHEA	MENOR- RHAGIA
Cauterization	0	0	0	0	0
Coagulation	1	6	4	6	1
Conization	0	0	3	0	1

TABLE VII. COMPARATIVE RATING

	CAUTERY	CONING	COAGULATION
Time for cure	1	3	2
Repetition of treatment	1	2	3
New cyst formation	1	3	2
Complications			
Stenosis	1	1	2
Inflammation	1	2	3
Menstruation	1	2	3
Final rating	1	2.2 (2)	2.5 (3)

COMMENT

The pathology present in this series of cases demonstrated that an inflammation of the cervix is seldom limited to the mucosa; it more commonly involves all the structures in the cervix and often extends into the lymphatics of the parametrial tissue. The glandular tubules in the cervical mucosa are occluded and filled with inflammatory exudate. The modalities used primarily destroy the cervical mucosa, either by cauterization, coagulation, or excision of tissue, but neither Nabothian cysts nor the lymphatic involvements are immediately affected, and it is therefore necessary to attack them independently. The cautery is best adapted to the treatment of Nabothian cysts, as well as for a cervical erosion when an erosion requires special treatment. The appearance of the cervix a few days after either cauterization, coagulation, or conization is practically the same, and the subsequent progress and healing after all three methods is almost identical. From the number of patients requiring destruction of newly formed Nabothian cysts during the course of observation after the first treatment, especially noticeable in those cases coned and coagulated, it seems that these glands are not completely removed with the mucosa. This may be due to a failure to remove enough tissue, or to the deep penetration of these glands. In either case, the healing of the mucosa in the canal forms an impenetrable roof, which sooner or later results in the enlargement of these glands, distended with a reaccumulation of inflammatory exudate. The fre-

The similarity of the three groups of cases permits a fair comparison. In evaluating the results, a patient was considered cured only when all symptoms had disappeared and the cervix was restored to normal. Such determinations necessitated prolonged follow-up and treatment, which in some cases extended over two years. In the group treated by coagulation such prolonged observations and treatment were carried out in all 50 patients. In the groups treated by cauterization and conization this was possible in only 44 patients. The other 6 in each group failed to reappear soon after the treatment was given, and could not be located thereafter.

DURATION FOR CURE

The time required to bring about a cure in each of the groups is indicated in Table IV. In order to bring about a cure in some patients, the same or one of the other technical procedures had to be repeated. Existing Nabothian cysts and cysts formed at a subsequent time required treatment. In every case, regardless of which modality was originally used, Nabothian cysts were destroyed by actual cautery.

TABLE IV. TIME REQUIRED FOR CURE

	CAUTERY	COAGULATION	CONING
Average	4 mo.	7 mo.	7.3 mo.
Shortest	2 mo.	2 mo.	2 mo.
Longest	12 mo.	31 mo.	19 mo.
Number in 2 mo.	19	10	5
Number in 3 or 4 mo.	13	15	10

In several of the cases developing cysts subsequent to the original treatment, repeated groups of cysts appeared at varying intervals. The number of patients requiring such additional treatment and the total number of times instituted, in the entire groups of patients, are shown in Table V.

TABLE V. ADDITIONAL TREATMENT

	REPEAT		CYSTS CAUTERIZED	
	SAME	OTHER	PREEXISTING	NEWLY DEVELOPED
Cauterization	0	1 (Cone)	22 cases	5 (4 cases)
Coagulation	2	4 (2 Caut.) (2 Cone)	9 cases	14 (9 cases)
Conization	2	3 (1 Caut.) (2 Coag.)	11 cases	18 (17 cases)

COMPLICATIONS

In no patient following cauterization in this series was any complication noted. In one patient treated by coagulation, bleeding from the cervical canal occurred after the slough had separated, but was easily controlled. In 6 patients following coagulation, stenosis of the cervical canal occurred, but in no case was the atresia absolute, and gradual

THE EFFECT OF SODIUM LACTATE IN RAISING THE CO₂ COMBINING POWER IN THE TOXEMIAS OF PREGNANCY

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IN NORMAL pregnancy, there is a depletion in the alkali reserve, as shown by the lowered CO₂ combining power. In the more severe toxemias, this alkali deficit is often aggravated, and tends to become uncompensated. That is, the pH of the blood, which has been very nearly constant, now is likely to fall.

Stander, Eastman and Harrison,¹ and Stander and Eastman² found that in eclampsia the blood pH falls as low as 7.0. This degree of acidity would, of itself, be fatal if long maintained. Furthermore, the authors cited have suggested that the high fetal mortality in eclampsia may be caused by the acidosis. These workers have shown that the marked acidosis of eclampsia seems to follow the convulsions, and if these be controlled, the patient can restore the blood pH to normal or nearly so. The explanation of the fall and subsequent rise in the blood pH and CO₂ combining power lies in the accumulation of organic acids, chiefly lactic acid resulting from muscular contraction, and ketone and other bodies. These acids are neutralized by the alkali reserve, giving their sodium salts. Thus the CO₂ combining power is diminished. After the convulsion, the sodium lactate is oxidized, and because of its ketolytic activity, so are ketone bodies. In this way sodium is again set free and is promptly bound as bicarbonate. The kidney, by excreting buffers and ammonia, releases still more sodium. Thus the alkali reserve rises. Meanwhile some of the sodium salts of these organic acids will be lost in the urine and deplete still further the blood alkali. Progressively then, the alkali deficit is aggravated, buffering power is lost, and the body is less able to combat the metabolic acids ordinarily and extraordinarily produced.

In the severe nonconvulsive toxemias, the CO₂ combining power often falls. Here, while the accumulation of organic acids is not so acute as in convulsions, the alkali depletion is progressive and the patient may be unable to regain the normal level of alkali reserve. If convulsions should occur, the resulting acidosis might be overwhelming.

In order to protect the patient from acidosis, an important feature in the treatment of toxemia of pregnancy has been to maintain or raise the CO₂ combining power. Glucose, with or without insulin, is widely used since its oxidation is ketolytic.

quency of partial cervical stenosis following coagulation may be due to an individual variation in the tissue resistance to the penetration of the current. This would influence the depth of coagulation produced with a standard amount of current. Too deep coagulation will cause excess connective tissue formation, with subsequent contraction and stenosis. The reason for the amenorrhea produced in some patients following coagulation is not clear.

SUMMARY

One hundred and fifty cases of cervical inflammation were treated by cauterization, coagulation, or conization of the cervical canal.

One hundred and thirty-eight cases were followed to a point of complete cure: that is, freedom from symptoms and eradication of pelvic pathology. Fifty were in the group treated by coagulation and 44 each in the groups treated by cauterization and conization.

The average length of time required to cure patients treated by cauterization was four months. Nineteen were cured in two months and 13 in three or four months.

The average length of time required to cure patients treated by coagulation was seven months. Ten were cured in two months and 15 in three or four months.

The average length of time required to cure patients treated by conization was 7.3 months. Five were cured in two months and 10 in three or four months.

Repetition of the same or one of the other methods was necessary in one case originally cauterized, in 5 cases originally coned, and in 6 cases originally coagulated.

Newly formed cysts developed and were treated in 4 patients originally cauterized, in 9 patients originally coagulated and in 17 patients originally coned.

Moderate stenosis of the cervical canal occurred in 6 patients treated by coagulation.

Acute inflammation of the tubes and ovaries developed in 4 patients treated by coagulation, and in 3 treated by conization.

Six patients treated by coagulation had subsequent periods of amenorrhea lasting from three to fourteen months.

CONCLUSION

From the discussion and summary, it is evident that all three methods are satisfactory for removing the diseased cervical mucosa.

The patients treated by cauterization are cured more quickly and with fewer complications than those treated by the other two methods.

Nabothian cysts and cervical erosions are best treated by cauterization.

The cautery is superior to the other two electrophysical methods for treating chronic cervical inflammations.

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In the present study, the molar lactate was diluted with distilled water in proportions up to 1:5, which is isotonic, and given by venoclysis. The dilution depended upon the amount of fluid which the patient was considered to need.

The CO₂ combining power of the plasma was determined in duplicate by the method of Van Slyke and Cullen,⁹ using the manometric apparatus. The blood was taken either without stasis or with minimal stasis. It was not drawn anaerobically, but was in the centrifuge within five minutes.

RESULTS AND DISCUSSION

In Table I are summarized all of the results of sodium lactate therapy thus far observed. The greatest discrepancy between the measured and calculated CO₂ combining powers is plus 7 volumes per cent in a patient who received 80 gm. of glucose just before, during, and after the lactate infusion. The mean difference for the whole group is plus 1.3 volumes per cent. Omitting patients who were given glucose, the greatest discrepancy is plus 5, the next minus 3; the mean difference between calculated and measured CO₂ is plus 0.5 volumes per cent.

It will be observed, in the last column of the table, that a rise in the level of blood uric acid is usually seen after sodium lactate is given intravenously. In view of the importance which has been attached to the blood uric acid as an indicator of liver function in the toxemias of pregnancy, this finding requires some explanation. Quick¹⁰ has shown that sodium lactate inhibits the renal excretion of uric acid. This would result in an increase in the blood level without necessarily meaning any

TABLE I. THE EFFECT OF SODIUM LACTATE IN RAISING THE CO₂ COMBINING POWER IN TOXEMIA OF PREGNANCY

DIAGNOSIS	CO ₂ C.P. BEFORE VOL. %	CO ₂ C.P. AFTER VOL. %	CO ₂ C.P. CALCULATED VOL. %	ERROR VOL. %	GLUCOSE GRAMS	URIC ACID CHANGE MG. %
Eclampsia	44	54	54	0	0	+1.4
Eclampsia (?)	12	42	36	+6	75	+9.5
Pre-eclampsia	30	48	46	+2	0	-1.2
Pre-eclampsia	32	39	38	+1	0	+1.4
Pre-eclampsia	38	57	55	+2	0	+1.1
Pre-eclampsia	32	51	48	+3	50	-2.1
Pre-eclampsia	36	61	54	+7	80	+1.9
Pre-eclampsia	35	51	51	0	0	-
Pre-eclampsia	36	44	47	-3	0	0
Pre-eclampsia	37	53	48	+5	0	-
Abruptio, oliguria	32	48	45	+3	350	+0.6
Abruptio, anuria, ure- mia, death	12	27	22	+5	50	Trans- fusion
	27	36	41	-5	0	
	32	38	40	-2	0	
	38	44	42	+2	30	
Terminal uremia	32	63	62	+1	0	
Pyelitis	36	50	49	+1	0	+0.2
Hydronephrosis	38	51	49	+2	0	
Hydronephrosis	33	50	48	+2	0	+0.1
Average				+1.3		+1.4

In the face of the primary alkali deficit, which has a tendency toward aggravation, glucose therapy may not be sufficient to raise or even maintain the alkali reserve.

Following this line of thought, Wilson³ treated 14 patients who had severe cases of toxemia with intravenous sodium bicarbonate. All showed favorable reactions, both clinically and in the increased CO_2 combining power of the plasma. Stander, Eastman and Harrison concluded from their detailed study of the acid-base equilibrium in eclampsia that glucose is inadequate, and recommend intravenous bicarbonate.

Since sodium lactate has several advantages over sodium bicarbonate, its usefulness in toxemia of pregnancy is suggested. These advantages of the lactate are:

1. Sodium lactate is easily sterilized, while bicarbonate is not. The latter decomposes to the caustic carbonate when heated above 80°C .

2. Sodium lactate releases sodium only as it is metabolized, thus changing the blood alkali more slowly and uniformly than would infused bicarbonate.

3. Sodium lactate is ketolytic, a molar solution being equivalent to 18 per cent glucose.

4. This treatment utilizes a normal physiologic mechanism, since large quantities of sodium lactate are found in the blood following exercise, and are metabolized.

In 1924, Haldane⁴ suggested the use of the sodium salts of acetic, citric, or other oxidizable organic acids as a means of raising the alkali reserve. The oxidation of the organic ion leaves sodium to be combined as bicarbonate.

Abramson and Eggleton⁵ studied in detail the utilization of infused sodium *r*-lactate. They showed that the metabolism of lactate was paralleled by an increase in the CO_2 of the blood.

Hartmann and Senn⁶ report the successful and satisfactory use of sodium *r*-lactate infusions in overcoming the acidosis of nephritis, diabetes, and dehydration. They believe that 60 per cent of the utilized lactate is oxidized at once, while 40 per cent forms liver glycogen. Abramson, Eggleton and Eggleton⁷ could not demonstrate the deposition of liver glycogen in the dog.

Hartmann and Senn⁶ have modified a formula derived by Palmer and Van Slyke,⁸ by which they calculate the dose of lactate required to produce a desired increment in the CO_2 combining power. It is assumed that 67 per cent of the body weight is water, and that the BHCO_3 is evenly distributed in that water and equal to the plasma level. One milliliter of molar sodium lactate, completely metabolized, will yield 1 ml. of molar sodium bicarbonate which will be equivalent to 22.4 ml. of CO_2 per liter. Therefore the expected increase in CO_2 , after sodium lactate, is:

$$\text{Increase (in volumes per cent)} = \frac{2.24 \times \text{ml. molar Na lactate}}{\text{Body wt. in kg.} \times 0.67}$$

Simplifying and transposing, this becomes:

$$(\text{Dose}) \text{ ml. of Na lactate} = 0.3 (\text{body wt., kg}) \times (\text{Vol. per cent desired increase in } \text{CO}_2).$$

For example, a patient weighing 60 kg. has a CO_2 combining power of 26. It is desired to raise the CO_2 to 40, *i.e.* by 14 volumes per cent.

$$\text{Dose (in ml. of molar lactate)} = 0.3 \times 60 \times 14 = 252.$$

In the example cited, if 252 ml. of molar lactate be given, the CO_2 should rise to 40. This expected level will hereafter be referred to as the "calculated CO_2 ."

ammonium chloride given in treating the supposed pyelitis. Since the metabolism of sodium lactate by normal subjects has been investigated in detail by authors cited above, further controls were not used. Of the toxemia patients, one was a pre-eclamptic; the other was a severe eclamptic whose CO_2 was increased from 12 to 42 volumes per cent by lactate, which also cleared up a four-plus ketonuria.

The lines describing the increase in CO_2 combining power seem to be straight. This would indicate that the rate of metabolism of the infused lactate is nearly constant. Since the lines appear to be straight over the period of the infusion, it follows that the lactate is metabolized at a rate independent of its concentration in the blood, at the levels with which we are concerned.

Since the lines shown on the graph are nearly parallel, it appears that the toxemia patients utilized the lactate as efficiently as did the normal subjects. This fact gives another answer to the possible objection mentioned above; i.e., that in toxemia the blood lactate is already elevated.

In at least six cases previous treatment with glucose, with or without insulin, had either been ineffective or had exerted its maximal effect in raising the CO_2 combining power. All of these patients showed the predicted rises in CO_2 when given lactate.

Usually the level of CO_2 established by the lactate was stable as shown by subsequent determinations of the CO_2 over a period of days.

Several of the patients had an increase in temperature and pulse rate and a hyperemia of the skin which appeared during the infusion and disappeared within four to six hours. The average dose of lactate given would result in the production of about 2 calories per kilogram per hour. This is about twice the basal metabolic rate for women of this group, and probably accounts for the temperature and pulse elevation.

The number of ante-partum patients who received lactate therapy for acidosis is much too small for any evaluation of the effect of the treatment in reducing fetal mortality. In the 5 patients carrying viable and living fetuses, all had living babies. In two other ante-partum cases, the fetus had died in utero before the lactate was given, and in one other the mother died undelivered in the fifth month of pregnancy.

SUMMARY

Sodium lactate has several advantages over sodium bicarbonate in the treatment of acidosis.

A series of patients with toxemia of pregnancy has been treated with sodium lactate intravenously. In all cases the CO_2 combining power was raised by amounts which had been closely predicted from the dose of lactate given.

The sodium lactate seems to be almost completely metabolized by the toxemic patient. This metabolism seems to be as efficient as in normal subjects.

An explanation is offered for the observations that following intravenous sodium lactate there is usually a rise in the blood uric acid, and

failure on the part of the liver to destroy its quota of uric acid arising from the metabolic processes. Fortunately, there is another consideration which militates against the interpretation that the lactate may be inhibiting an already impaired liver. In two of the patients, the icteric index was elevated to about 15. Following the lactate infusion, the index fell in both of these. It might be pointed out again that 40 per cent of the lactate is thought to form liver glycogen, and thus has a favorable effect upon that organ. This deposition of glycogen is one of the ends in view when glucose is given in treating toxemia. Furthermore, Hartmann and Senn⁶ have shown that patients with marked liver damage utilize the lactate about as well as normals.

The close agreement between the expected and actual effect of the lactate upon the CO_2 indicates that the lactate is practically all metabolized. This fact partially answers what we had considered as a possible objection to the use of sodium lactate in toxemia therapy. Stander and

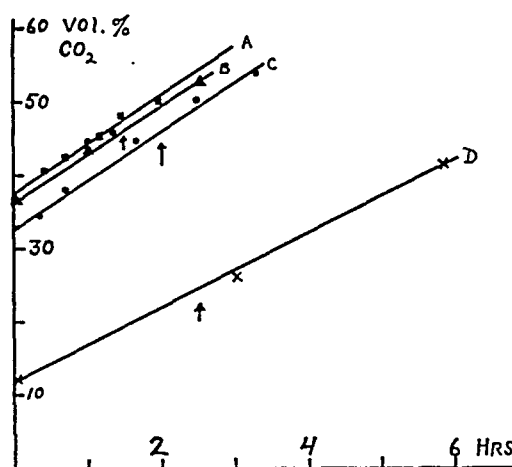


Chart 1.—The rate of increase in CO_2 combining power of the plasma after intravenous injections of sodium lactate. A and C (■ and ●) are normal subjects. B (▲) pre-eclamptic patient. D (×) eclamptic patient.

Radelet¹¹ observed that in toxemias of all groups the blood lactate is elevated. This was interpreted as a possible indication of an upset in carbohydrate metabolism, probably concerned with the synthesis of glycogen from lactate.

Hartmann and Senn⁶ found in diabetes, nephritis and dehydration that the measured CO_2 usually fell short of the expected level. In some of their cases, as much as 18 per cent of the infused lactate was lost in the urine, and was thus not available for metabolism. Perhaps the oliguria present in most of our toxemia patients limited the renal excretion of lactate, and is responsible for the apparently more complete utilization.

The rate of increase in CO_2 combining power, which is proportional to the rate of metabolism of the lactate, was followed in some cases. In Chart 1 is shown the rise in CO_2 combining power in two "normals" in comparison with two toxemia patients. The "normals" were cases of hydronephrosis whose CO_2 combining powers had been driven down by

19-year-old amenorrheic female, Fauvet¹⁶ obtained prolan A effects in the urine before operation and a prolan A and B reaction postoperatively. In another case menstruating normally, he¹⁶ found the urine to be negative both pre- and postoperatively. Implants of the tumor into immature rats were also negative.

The case here reported is another to be added to the literature and represents the first in which the extracts of the tumor for estrogenic and gonadotropic hormones were studied.

CASE REPORT

G. A., colored, 16 years old, nullipara, was admitted to the Gynecological Service of the Lincoln Hospital complaining of a mass in the abdomen. Her past history was essentially negative except for an attack of mumps one month before admission to the hospital. Her menstruation had always been regular and had begun at the age of twelve. There were no symptoms referable to the mass. Physical examination showed a well-developed and well-nourished female, perhaps slightly more mature physically than her age indicated. Her breasts were normal and showed no secretion. Her hair distribution was that of a normal female. On pelvic examination the external genitalia and vagina were found to be normal. The cervix was conical, closed, pointed posteriorly and was slightly eroded. A firm, nontender mass, smooth in contour, and moderately movable, was found in the right fornix. It extended above the pelvis to the left of the midline and about 1 inch above the umbilicus. To the left of this mass a similar structure believed to be the uterus could be felt. The left fornix could not be palpated and adnexa as such were indistinguishable.

Laboratory examinations, including Wassermann, were essentially negative. X-ray examination of the lungs and sella turcica was negative. Uterosalpingography, by means of iodized oil, was attempted but the results were inconclusive. At laparotomy the right ovary was found to be completely replaced by a large, solid tumor. The left ovary was normal in size but contained a small nodule upon its surface in the region of one of the poles. The other abdominal viscera and the peritoneum were normal. Both ovaries were removed.

Convalescence was complicated by lobar pneumonia and a transitory pyelonephritis. The patient was discharged twenty-three days after operation and was referred for x-ray therapy. She was seen four months after leaving the hospital and examination of the pelvis was found to be essentially negative. She felt well and had no complaints. A Friedman pregnancy test on the urine at this time was negative.

PATHOLOGIC REPORT

Gross.—Specimen consisted of both ovaries which had been removed in toto. The right ovary was the site of a kidney-shaped tumor measuring 20 by 12 by 7 cm. and weighing 1,343 gm. It was encapsulated and its external surface was smooth and irregularly nodular. Its color was homogeneously yellowish gray, with several mottled hemorrhagic areas. On section, its consistency was found to be rubbery throughout, and its appearance lobulated. A whitish, oily fluid could be scraped from its cut surface. Normal ovarian tissue was nowhere to be found.

The left ovary measured 4 by 2.5 by 1 cm. and was essentially negative except for a small area measuring about 1 cm. in diameter, situated on its surface near one of its poles. On section this area closely resembled the tissue present in the right ovary. The nodule was circumscribed and projected above the surface of the ovary to some degree.

Microscopic examination of the right ovary showed large collections of cells which stood out clearly and stained well (Fig. 1). The cells were surrounded by connective tissue septa dividing them into lobules which varied in size, some being large and others small. Projecting from the larger fibrous septa were smaller fibrous bundles which dipped down into the lobules dividing them into smaller and smaller units, so that the final subdivisions consisted of collections of only 6 to 10 cells. The fibrous tissue was relatively dense, and scattered irregularly throughout its meshes many lymphocytes

an increase in the body temperature and pulse rate. All of these are transitory, and are not considered as contraindications to the use of lactate.

We wish to acknowledge our indebtedness to Drs. S. A. Cosgrove, J. F. Norton and E. G. Waters for their interest in this work, and for permission to use patients on their services. Dr. Cosgrove also read and criticized the typescript.

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HORMONAL BIO-ASSAY IN A CASE OF OVARIAN DISGERMINOMA

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DISGERMINOMA of the ovary was first described in 1906 by Chevassu¹ who called it "seminoma" because of its resemblance to male testicular tissue. Since that time numerous cases have been reported in the literature. In recent years R. Meyer² has applied the logical term "disgerminoma" to it to suggest an origin from a mal-development within the gonad. It may therefore involve either the ovary or the testicle. Among those who have discussed the condition R. Meyer,³ Fauvet,⁴ H. O. Neumann,⁵ Geist,⁶ and Meigs⁷ may be mentioned. In the cases described the clinical as well as the pathologic features were extensively discussed.

Hormonal studies which are of extreme importance in solid ovarian tumors in general and in disgerminoma in particular have, however, been lacking. The only instances in which the tumors themselves were studied for the presence of hormones included a case by Gospe⁸ of a granulosa cell tumor in which estrogenic hormone was found, a similar case by Schuschania,⁹ and others by Meyer,¹⁰ Klasten,¹¹ and Neumann.¹² In the theca cell tumor group the only case studied was that of Geist and Spielman,¹³ who found considerable quantities of estrogenic hormone. For the arrhenoblastoma, Szathmary¹⁴ found complete absence of both estrogenic and gonadotropic hormones in the urine of one case. The appended chart (Table I) includes all studies from the point of view of hormones up to the present time. In some of the cases of disgerminoma attempts were made to study the gonadotropic hormone in the urine. The results have proved to be interesting. Bluemel¹⁵ collected the results obtained in the hormonal investigation of the urine of 15 cases occurring in the male testicle. In 11 cases a prolan A reaction was obtained. In a twelfth case, in addition to prolan A, following the removal of the involved testicle and the occurrence of metastases, prolan B was also demonstrated. Implants of the metastases in this case showed both prolan A and B. In a

was situated near the surface of one of the poles. The nodular area here showed essentially the same characteristics as those of the right ovary, except that the cells rather than the connective tissue predominated. The cells of the nodule were not nearly as clearly stained, and most of the cytoplasm did not appear at all. Instead, large vacuoles were seen. The nuclei did not stain as clearly as those of the cells of the other ovary. The fibrous tissue contained small round cells but their number was not as great as those of the other side. The rest of the ovary showed the typical structure of ovarian tissue. However, ova were not present, nor could follicles either in the process of maturation or atresia be recognized. Several corpora albicantia and normal corpora lutea were present. Fat stains showed only a small quantity of fat distributed both within and outside of the cells.

HORMONE STUDIES

Extracts of the tumor tissue were studied for hormonal content. For the gonadotropic hormone the acetone method described by Frank and Salmon¹⁷ for extraction of blood was utilized. For the estrogenic

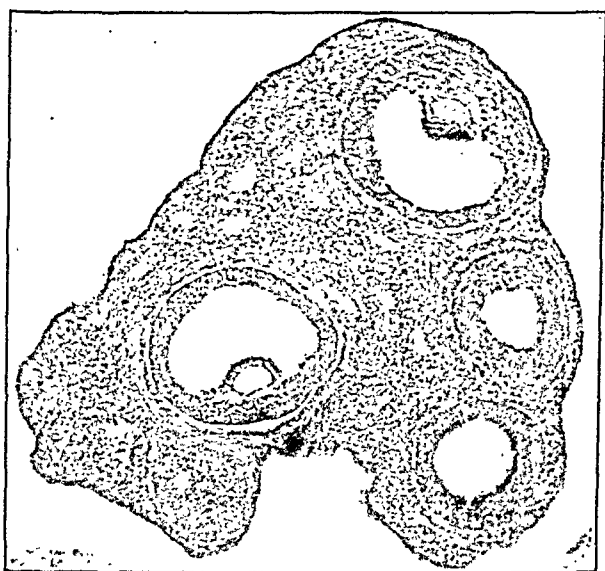


Fig. 3.—Immature rat's ovary showing follicular ripening (A.P.R. I.).

hormone the extracts were prepared by using lipid solvents consisting of alcohol and ether. Gonadotropic hormonal extracts injected into immature rats showed a prolant A affect (A. P. R. 1) with the equivalent of 24 gm. of tissue (Fig. 3). A total of 60 R.U. of prolant A was therefore present in the entire tumor. Extracts for estrogenic hormone injected into castrated mice showed consistently negative vaginal spreads indicating a complete absence of the estrogenic hormone.

DISCUSSION

Table I shows hormonal studies performed upon either the urine of patients harboring solid ovarian neoplasms or the tumors themselves. As can be seen, relatively little work has been reported up to the present time. For the granulosa cell tumors there is considerable evidence that the estrogenic hormone is present in the tumor itself as can be seen by the positive results obtained from extracts of the tumor,

were to be seen. In all portions of the tumor, the connective tissue dipped down and formed the supporting tissue for the cells.

The cells forming the tumor were large and their nuclei varied in size. In some the nuclei occupied almost the entire cell, so that only a rim of cytoplasm was distinguishable. In others, the nuclei were smaller, in the main centrally situated, and occasionally did not stain well. In the nuclei, at least one nucleolus could be made out. The larger nuclei stained heavily and appeared granular. The cytoplasm of the cell took a much lighter stain which was homogeneous and somewhat reticulated.

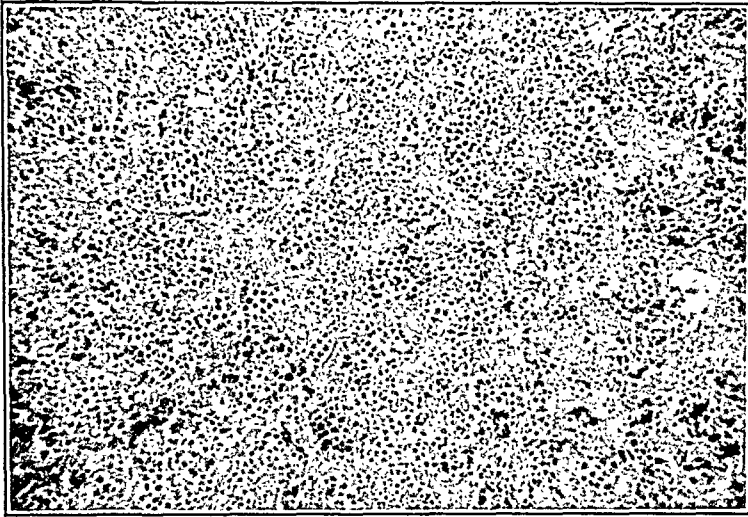


Fig. 1.—Right ovary, low power, showing the large clear cells divided into lobules as well as the large amount of connective tissue containing lymphocytes.



Fig. 2.—Left ovary. Low power. The tumor nodule situated at one pole stands out clearly. Normal ovarian tissue is sharply demarcated. The rich blood supply around the tumor is evident.

As has been mentioned, the small round cells were irregularly scattered throughout the connective tissue. An occasional large round cell, eosinophile and plasma cell, was also seen. There were no multinucleated giant cells visible. In some sections there had been considerable degeneration of the cells as well as pyknosis of the nuclei and in others the connective tissue were hyalinized. Normal ovarian tissue was nowhere to be found in this ovary.

Microscopic examination of the left ovary (Fig. 2) showed only one small nodular area which was the site of the tumor. This area was well demarcated from the rest of the ovarian stroma by connective tissue, which contained numerous blood vessels and

from implants, and from urinary titration. The theca cell tumor in which considerable estrogenic hormone was found by Geist and Spielman¹³ suggests a definite relationship to the granulosa cell group.

The findings in disgerminoma of the ovary appear to point to an increase in prolan A. Bluemel's¹⁵ and Fauvet's¹⁶ reports showing A. P. R. I to III reactions in the urine of a male on the one hand, and a female on the other, suggest hormonal activity on the part of the tumor. This is further emphasized by the presence of prolan A in the authors' case. The significance of the isolation of this hormone in cases of disgerminoma is not clear. When associated with cases of amenorrhea in which developmental anomalies may play a part, an increase of the prepituitary hormone either in blood, urine, or the tissues themselves may be expected since an increase in the quantity of this hormone has repeatedly been observed in amenorrheic females.

Its presence, however, in males (Bluemel¹⁵) as has been stated, implies hormonal activity on the part of the tumor. No satisfactory conclusions, however, can be drawn at the present time because of the paucity of material reported heretofore, especially since there are no reports of the gonadotropic hormone content of normal tissues. It is to be emphasized that hormone studies in cases of solid ovarian tumors offer the greatest hope for clarification of the entire subject of neoplasms of the ovary.

SUMMARY AND CONCLUSIONS

1. A case of disgerminoma of both ovaries in an otherwise normal 16-year-old colored girl is presented.
2. Hormonal studies upon extracts of the tumor, the first to be reported in this type, showed complete absence of estrogenic hormone and the presence of the prepituitary hormone (prolan A).
3. Since embryologically the tumor may be traced to certain undifferentiated neuter cells in the primitive ovary the absence of estrogenic hormone is to be expected. The presence of the prepituitary hormone, however, cannot be accounted for.
4. It is emphasized that hormonal studies in cases of ovarian neoplasms offer the greatest hope for clarification of the subject.

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TABLE I. HORMONE STUDIES OF SOLID OVARIAN TUMORS*

TUMOR	AUTHOR	BLOOD STUDIES		URINE STUDIES		TUMOR STUDIES	
		E.S.	A.P.R.	E.S.	A.P.R.	E.S.	A.P.R.
Granulosa cell tumor	Meyer, 1931		A.P.R. 0	Pos. (pre-op.)	A.P.R. I	Pos. (im) Neg. (ex)	(im) Neg. Neg.
	Schuschania, 1930			Neg. (post-op.)	111 (9 days post-op.) Neg (later)		
	Pahl, 1931					(ex) Pos. (im) Neg. (ex) Pos. (im) Pos. (ex) Pos.	
	Klaften, 1932						
	Kaufman, 1932						
Arrhenoblastoma	Frank, 1932			Pos. (7 days post-op.)	A.P.R. I	(ex) Pos. (im) Neg. (ex) Pos. (im) Pos. (ex) Pos.	
	Neumann, 1933	Pos.	A.P.R. I				
	Dworzak and Podleshka, 1933			Pos. (pre-op.) Neg. (post-op.)	I (pre-op.) Neg. (later)	(ex) Pos. (im) Pos. (im) Neg.	
	Kleine, 1934						
	Gospe, 1936						
Disgerminoma	Wagner, 1930			Neg. (pre-op.)			
	v. Szathmary, 1934			Pos. (1 day post-op.)	Neg. I to III		† I to III
	Wallis, 1933				A.P.R. I (pre-op.)		
	Kleine, 1934				A.P.R. I & III (4d post-op.)		
	†Blumel, 1934				Neg. (pre- and post-op.)	(im) Neg.	
Theca cell tumor	Fauvet, 1936					(ex) Neg. (ex) Pos.	A.P.R. I
	Authors, 1937						
	Geist and Spielman, 1935						

*E.S., Estrogenic substance. A.P.R., Anterior pituitary reaction. (im), Implant. (ex), Extract. †, Performed on metastatic tumors. Pos., Positive reaction. Neg., Negative reaction.

We, therefore, felt that some useful information might be gained from serial x-ray studies after barium meals during labor. Schaefer and Guthmann and Stähler have made roentgen studies on a number of women in various stages of pregnancy and the puerperium, but on none during labor. At term they found distortion and displacement of the stomach always present. Gastric activity was almost always altered, but inconstantly so. In part of their cases the stomach was flaccid with sluggish peristalsis, in the others peristalsis was increased. In either circumstance evacuation was rapid or normal, never taking more than three hours. The duodenal bulb could not be visualized.

METHOD

Our procedure has been to give six ounces of a thin barium mixture, and, after an immediate exposure, sometimes with fluoroscopy, to take three or four pictures at hourly intervals. The x-ray examinations were made with the patient standing, but she was kept in bed during the rest of the test period. No food, fluid, or medication was allowed. The length of the observation period and the necessity of the patient's cooperation made it obligatory to select primigravidas in whom delivery seemed not too imminent. None of the patients had previous histories suggestive of gastrointestinal disorders with the exception of some limited vomiting of early pregnancy in several instances. They were in active first stage labor of varying intensity. The earliest delivery occurred after barium was five hours, the latest thirty-eight hours. The results from the ten cases on whom we were able to obtain significant data are summarized in Table I.

TABLE I

CASE	HOSP. NO.	AGE	AT BEGINNING OF TEST		EVACUATION TIME AND COMMENT	TIME OF DELIVERY AFTER BaSO ₄
			DILATATION	PAINS		
1	E. H. 18636	34	2-3 F.B.	Mod. 5-8 min.	Empty in 2 hr.	26½ hr.
2	A. R. 19058	22	1 F.B.	Irreg. 4-8 min.	Empty in 3 hr. Sl. residue delineating mucosa.	24 hr.
3	A. S. 18641	26	2 F.B.	Irreg. 4-8 min.	Empty in 2 hr.	16 hr.
4	V. B. 18652	22	2½ F.B.	Mod. 4 min.	Empty between 3-4 hr. Sl. residue along lesser curvature.	9 hr.
5	M. C. 18864	25	1 F.B.	Mod. 5 min.	Empty in 2 hr.	17 hr.
6	H. M. 18870	22	3-4 F.B.	Mod. 3-4 min.	Empty between 2-3 hr.	5½ hr.
7	M. G. 18930	26	2½-3 F.B.	Short 5 min.	Empty in 2 hr.	38 hr.
8	I. M. 18977	26	2 F.B.	Mod. 5 min.	Empty between 3-4 hr. with sl. residue	16½ hr.
9	A. W. 18912	26	3 F.B.	Mod. 3-5 min.	About 50 per cent residue at 4 hr. Apparent increase between 2-3 hr. ? Ingestion of fluid.	6½ hr.
10	O. N. 18831	34	3-4 F.B.	Mod. 4-5 min.	At 1 hr. major portion of meal still in situ. No further pictures. After delivery vomited approximately all of test meal.	5 hr.

AN X-RAY STUDY OF GASTRIC FUNCTION DURING LABOR*

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THIS study was undertaken because it has long been our opinion that gastric digestion is often arrested during labor. The frequency of vomiting, particularly during or after anesthesia, of food which from the patients' statements, we know had been eaten many hours earlier, inevitably leads to such an impression. This observation is common among anesthetists with wide delivery room experience.

Could it be shown that there is, in general, delayed emptying of the stomach during labor, it would open for serious consideration two problems; first, a revision of the common methods of maintaining patients' nutrition and water-balance during labor, and, second, the adoption of steps to prevent vomiting during anesthesia when it is suspected that recently ingested material remains in the stomach.

Emesis during or directly after anesthesia is a definite cause of the serious post-partum complications, pulmonary atelectasis and aspiration pneumonia. These complications are not common, but none the less important. In a review of morbid cases for the past eleven years among 20,351 deliveries at the Methodist Episcopal Hospital, we found but 7 that were unquestionably aspiration accidents. The true incidence is probably higher. There has been no indexing of aspiration accidents as such. There were no fatalities. We know of two cases elsewhere in which the aspiration of vomitus during delivery caused sudden death.

In any case, vomiting is dangerous, interferes with anesthesia, and occurs all too frequently in obstetric as compared to surgical anesthesia. It is not unlikely that the same causative factors contribute to another occasional intra- or post-partum complication, namely, acute dilatation of the stomach.

We have been able to find no factual observations on gastric function during labor in the obstetric literature for the past twenty years. The authors of several textbooks points out that vomiting may occur during labor and be a disagreeable feature of anesthesia, but gastric retention has apparently not been considered hazardous. In general, they recommend that solid food be omitted but fluids given more or less freely until late in labor. In only one instance is a proscription of even fluid by mouth in the latter first stage advised.

*Presented at a meeting of the Section on Obstetrics and Gynecology, New York Academy of Medicine, May 25, 1937.

GRANULOSA CELL TUMORS OF THE OVARY WITH PRECOCIOUS PUBERTY

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IN THE 45 cases of malignancy of the ovary proved by microscopic examination at the Wisconsin General Hospital during the past eight years, five have been granulosa cell tumors. The age incidence in these cases has varied from five to sixty-four years. No case of bilateral involvement of the ovaries has been encountered. Every case, except that of a five-year-old girl, was treated by surgical removal of the tumor followed by x-ray therapy. There has been no known recurrence of the tumor in any of the cases. A summary of the 5 cases is given in Table I.

The particular purpose of this paper is to outline the influence of granulosa cell tumors on preadolescent girls and to report a case occurring in a five-year-old patient.

CASE REPORT

History.—D. M., aged 5 years, 2 months, was admitted to the Wisconsin General Hospital on Jan. 13, 1936. She was born two weeks prematurely by forceps delivery of a 27-year-old mother, who at the time of the child's birth had had high blood pressure and albuminuria for one month. Birth weight was 5 pounds, 4 ounces. She developed normally until June, 1935, at which time her breasts began to enlarge and pubic hair began to appear. In September, 1935, following a day of mild abdominal pain, she began to have a slight bloody vaginal discharge. Except for four or five intervals of ten to nineteen days of amenorrhea following each injection of "follutein" given by her family physician, her menstrual flow remained constant. Her breasts continued to enlarge. Her facial expression became more mature. During the six months prior to her admission to the hospital, she gained about eight pounds in weight.

Physical Examination.—Patient was a well-developed, well-proportioned child about the size of an 8 year old. Height 46 inches. Weight was 51 pounds. Optic fundi were normal. Blood pressure was 116/74. Breasts and nipples were well developed. There was an abundant growth of pubic hair. There was no axillary hair. Her hips were wide. The abdomen was slightly protuberant. An ovoid tumor about 8 by 5 cm. was palpable in the right lower quadrant of the abdomen.

Laboratory Findings.—Urinalysis, blood counts, blood sugar, and nonprotein nitrogen were normal. X-ray plate of the cranial bones was normal. Bone age, as determined by the carpal bones, was that of a child of at least 10 years. Aschheim-Zondek test was negative. No blood or urine studies for estrin were performed. Intelligence quotient was 125.

Impression.—Granulosa cell tumor of the right ovary.

Treatment.—Right salpingo-oophorectomy was performed on Jan. 31, 1936. The left ovary was normal. The uterus was slightly larger and softer than normal.

Pathology.—Right ovarian tumor measured 8 by 5 by 4 cm. It had a grayish, granular, somewhat solid, fibrous cut surface with a thick capsule. Microscopically this was a cellular tumor with granulosa cells diffusely scattered throughout the fibrous stroma. There was a tendency to form cords and nests of cells. Small and moderate sized cysts were seen to be lined by several layers of cells.

Postoperative Progress.—Beginning on the second postoperative day, a profuse menstrual flow lasted for forty-eight hours. After the eighth postoperative day there was no discharge from the vagina. By the twenty-fourth day the breasts

DISCUSSION

It is seen that of the completed cases but one, Case 9, shows any appreciable delay in gastric evacuation. There is some suspicion in this case that the patient may have, in addition, taken some fluid, for there was apparently an increase in the stomach contents between the last two exposures. Case 10 is included for interest, though the x-ray findings are incomplete. One hour after administration the shadow of the barium meal had not appreciably diminished. This was true in no other instance. It was impossible to take further pictures, but following delivery, five hours after the barium, she vomited what seemed to be the entire test meal.

From this small series we can say only that there is no constant or characteristic alteration of gastric evacuation in primigravidas during labor. Delay apparently occurs in some patients as an individual disturbance. There was no evidence of obstructive interference in the cases with retarded emptying. The changes are probably functional and neuromuscular rather than mechanical. Whether there may be any correlation between the severity of labor pains and the incidence of gastric dysfunction is not indicated by our data. What effect the various drugs used for amnesia and analgesia may have on gastric activity merits study.

Despite the evidence that not all patients have gastric retention during labor, we believe that the occasional arrest of digestion as demonstrated above and observed clinically warrants considerably caution in administering even fluids by mouth to any patient in active labor, although it may therefore be necessary to increase the use of parenteral solutions. When a patient has a short labor and comes to delivery after a recent meal, or when it is suspected that the stomach has not been emptied of food or fluids taken some time before, it would doubtless be wise to evacuate her stomach by lavage before giving anesthesia. We are not yet sanguine enough to suggest this as a routine for the busy delivery room; it is only the hindsight from the occasional aspiration catastrophe that strongly recommends it.

SUMMARY

1. Of 10 primigravidas studied by G-I series during labor, two showed delayed, the rest normal, gastric evacuation.

2. Since it seems that some individuals may, unpredictably, have gastric retention in labor, it is recommended that the oral route for the upkeep of nutrition and fluids be recognized as sometimes inefficient and potentially hazardous, and that precautions be exercised to avert vomiting during anesthesia.

The expenses of this study were borne by the Edwin F. Lindridge Fund.

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were definitely smaller in size. A second Binet test on the twenty-fifth postoperative day showed her intelligence quotient to be 125. Re-examination on June 11, 1936, showed that there had been a definite regression of secondary sex characteristics. The pubic hair had practically disappeared and the breasts were much smaller in size. The patient was seen again on May 4, 1937. She had had no vaginal discharge. Her breasts were normal. The nipples were not prominent. No pubic hair was present. Her body configuration was that of the childhood type. The abdominal

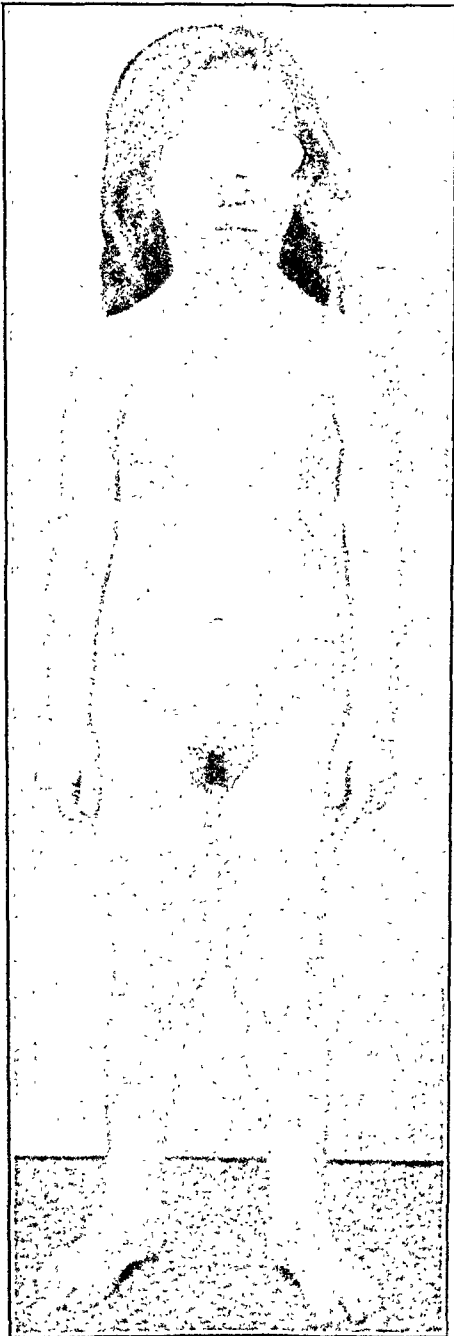


FIG. 1.

FIG. 1.—Precocious secondary sex characteristics in a 5-year-old girl with a granulosa cell tumor of the right ovary.

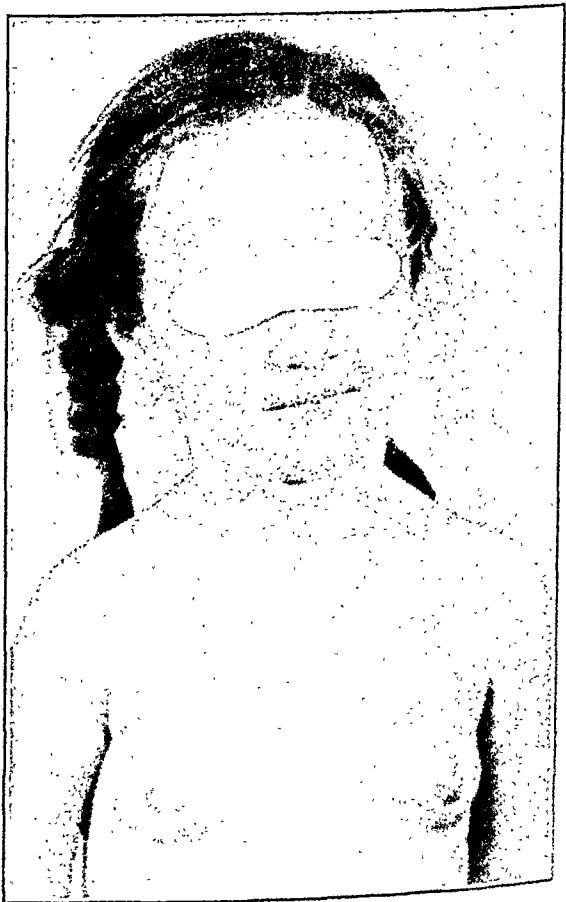


FIG. 2.

FIG. 2.—Precocious breast development resulting from a granulosa cell tumor in a 5-year-old patient.

TABLE I. SUMMARY OF FIVE CASES OF GRANULOSA CELL TUMOR OF THE OVARY FROM THE WISCONSIN GENERAL HOSPITAL

PATIENT	AGE	SYMPTOMS	GROSS PATHOLOGY	HISTOLOGY	TREATMENT	PROGRESS
D. M.	5	Continuous bleeding for 5 months	Right ovarian tumor 8 by 5 by 4 cm. Thick capsule	Mixed type	Right salpingo-oophorectomy	Regression of puberty precox. Well after 15 months
L. W.	35	Irregular menses for 6 years. Menorrhagia. Four months' continuous bleeding	Left ovarian tumor 16 by 12 by 7 cm. Well encapsulated	Solid masses granulosa cells. Hyperplasia of endometrium	Curettag, left oophorectomy, uterine suspension, x-ray therapy	Well after three years
T. L.	43	Amenorrhea 1 year. Menorrhagia for 1 year. Continuous flow for 5 years	Right ovarian tumor 22 by 17 by 12 cm. Well encapsulated	Solid masses of granulosa cells. Endometrial hyperplasia	Curettag, right salpingo-oophorectomy, supravaginal hysterectomy, x-ray therapy	Well after one year
A. C.	52	Brownish discharge 1 year. Continuous bleeding 3 weeks	Left ovarian tumor 6 by 5 by 5 cm.	Solid cellular tumor. Endometrial hyperplasia	Curettag, colporrhaphy, left oophorectomy. Fixation of uterus. X-ray therapy	Well after three years
E. F.	64	Menopause at 45. Regular menses resumed at 64 for 6 months. Continuous flow for 1 month	Large thin walled left ovarian tumor filling the abdomen	Uniform masses of granulosa cells. Low grade malignancy	Transfusion, excision of ruptured left ovarian tumor, x-ray therapy	Discharged in good health 20 days after operation. No follow-up examination

influenced by puberty precox. Arnold Gesell, after thorough mental studies of cases of precocious pubescence, concluded that sexual precocity had no marked effect on mental maturation. Mentality of two of the eight reported cases of granulosa cell tumors in children was definitely low. The usual abdominal finding is an unilateral tumor of the ovary. Each of eight reported cases had a palpable tumor. Aschheim-Zondek test may be positive. The excess of estrin produced by these

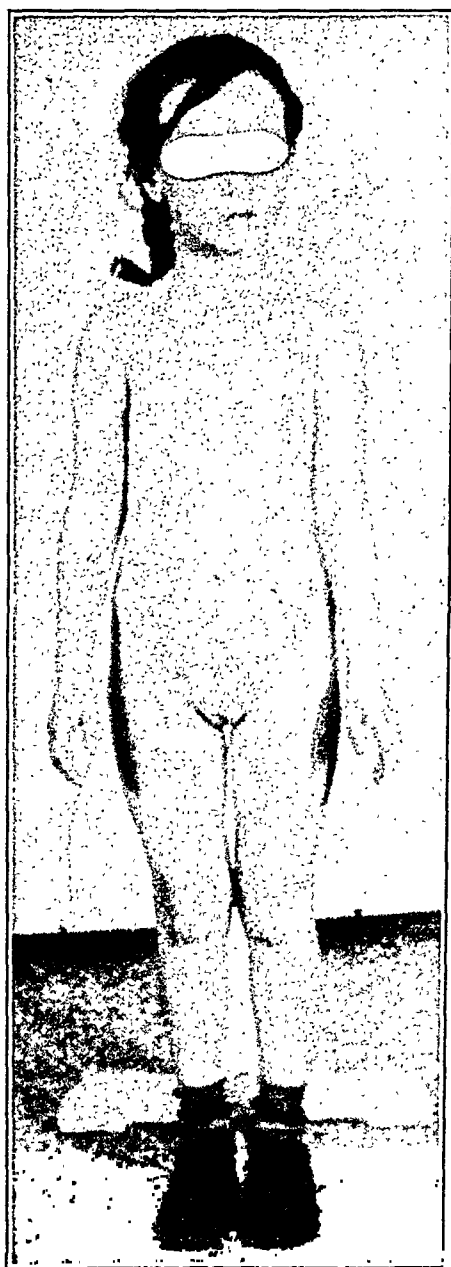


Fig. 4.—Recession of secondary sex characteristics fifteen months after removal of a granulosa cell tumor of the right ovary.

tumors is considered by Novak to be one of the strongest evidences of the direct rôle played by the female sex hormone in the normal production of sex characters.

Differential diagnosis is usually not difficult. Teratoma of the pineal body is a very rare cause of female sex precocity. Suprarenal adenomas and hypernephromas cause, in children, remarkable somatic growth and precocious development of the sex organs, but rarely cause premature menstruation. In basophilic adenomas of

wound was well healed. The uterus on bimanual examination was found to be small, forward, and movable. The fornices were clear.

DISCUSSION

A summary of the literature up to February, 1936 revealed only eight reported cases of granulosa cell tumors of the ovary causing symptoms in children under

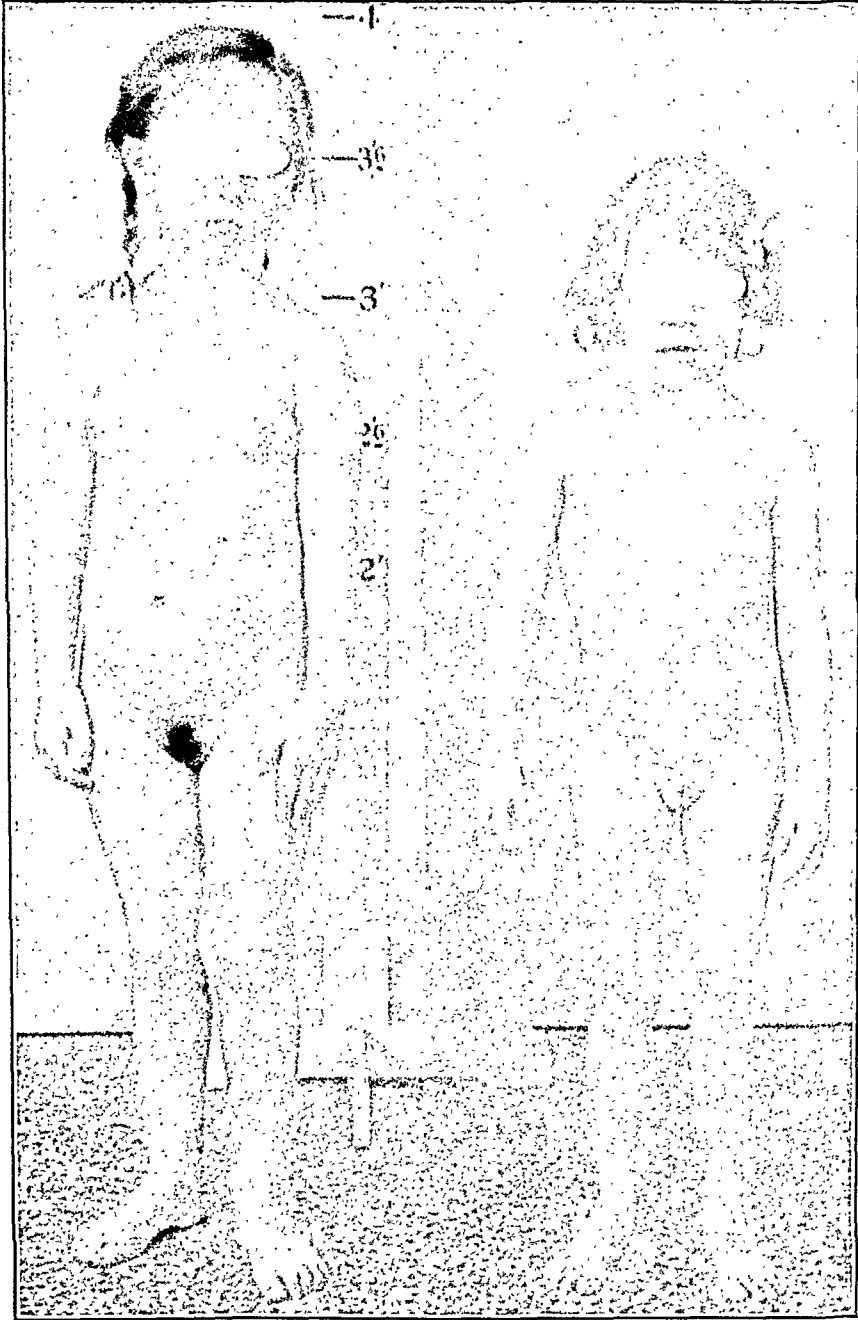


Fig. 3.—Skeletal growth compared with that of a normal 5-year-old patient.

ten years of age. Kleine has reported the youngest case with symptoms beginning at three years and five months. Practically all cases have shown the same symptoms and physical signs exhibited by the patient described above. The usual symptoms are: menstrual bleeding, marked acceleration of skeletal growth, hypertrophy of the breasts, and the development of pubic and axillary hair. Mental age is not

GRANULOSA CELL TUMOR OF THE OVARY*

REPORT OF A CASE FOLLOWED BY PREGNANCY

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TUMORS having a functional role, or an endocrine influence, offer an ever more interesting field; not particularly because of their rarity, but because of the possible insight which may be gained in regard to abnormal functions of the endocrine glands.

Credit for our present interest in these tumors must be given to Robert Meyer,¹ who enlightened us on the subject especially in 1930. An adenoma of the Graafian follicle, with transition to malignancy, was first observed in 1895 by von Kahlden.² Others described tumors with follicle-like areas, but no proof was given of their granulosa qualities except by von Werdt³ in 1914. Meyer, about the same time, definitely classified these neoplasms which had the characteristics of follicular epithelium into the granulosa cell group.

As to origin, the consensus of opinion leads one to accept the view of Fischel that ovarian mesenchyme is the forerunner of normal granulosa cells. Not until this genesis is established can we hope for definite proof of the origin of granulosa cell tumors, but at present, both are considered to arise from the mesenchyme of the ovarian anlage.

Of the ovarian tumors, the granulosa cell type has been found to comprise 0.9 per cent (Szathmary), 1.4 per cent (Fauvet), and 4.04 per cent (Klaften), or an average of 2.11 per cent in a series of 1,728. The majority of cases, out of a total of approximately 250, are unilateral. The incidence in 200 cases collected by Pratt⁴ was maximal between the ages of 45 and 54 years, though they may occur at any age.

CASE REPORT

Miss C. D., 36 years of age, was admitted to the Charity Hospital on May 8, 1937. She complained of "almost continuous menstruation." Menses began at the age of 12 and were of the twenty-eight-day type, lasting six or seven days, profuse the first two days and scanty the remainder, until she reached 26 years of age. From this time to the age of 35 years, the periods occurred every three or four months, were scanty, and lasted only two days. Beginning in April, 1936, the patient noticed varying degrees of vaginal bleeding, requiring 8 napkins on some days and only 1 on others, except for two brief intervals. She states that she was given injections of either theelin, antuitrin-S, or progynon every two weeks from April to October, 1936, a tonsillectomy was performed and ergot was taken, all without noticeable effect. However, on stopping treatment, there was no bleeding until January, 1937. During this period of amenorrhea, she noticed that an aching pain, which had previously been present in the right lower abdomen, became "sore like an abscess" and radiated down the right thigh. The pain had since been intermittent

*Read before the New Orleans Gynecological and Obstetrical Society, April 21, 1938.

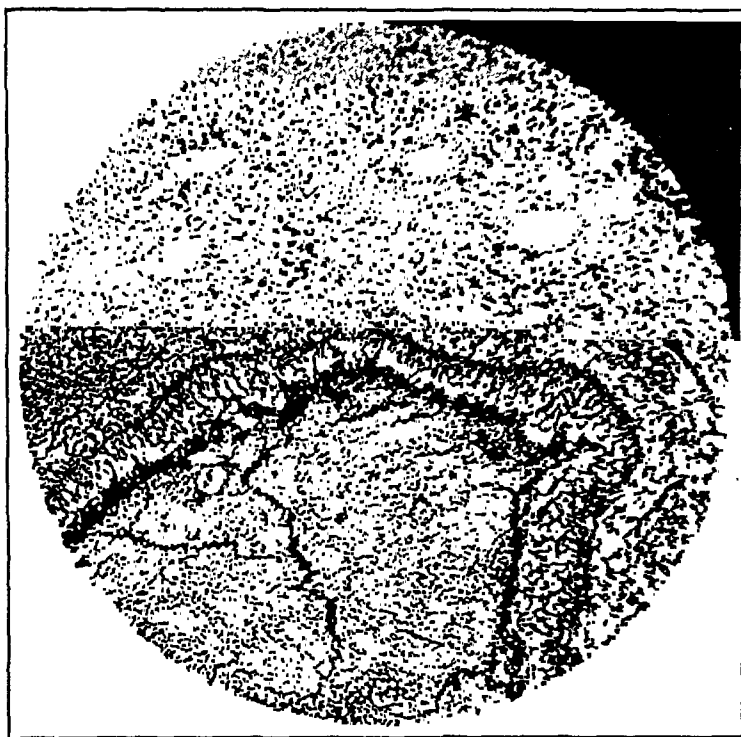


Fig. 5.—Granulosa cell tumor, low power $\times 100$.

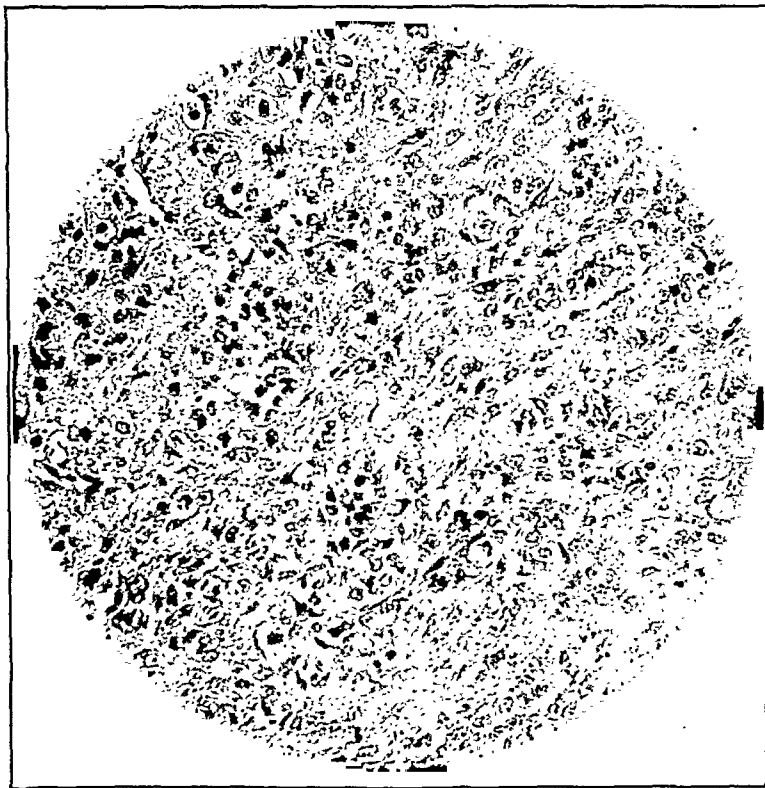


Fig. 6.—Granulosa cell tumor. High power $\times 300$.

the pituitary, the patients are usually quite fat, changes in the eye grounds are frequent, and hirsutism is usually not a marked feature.

Complete surgical removal of a granulosa tumor from a child brings about a rather rapid regression of all precocious sexual characteristics.

consulted. She returned to the hospital and received 6 daily injections of a luteinizing hormone, which caused a cessation of bleeding after two days. On August 11, September 8, and October 8, normal menstruations occurred, lasting six days. The patient married September 21, "thinking her troubles were over." However, the next period was delayed until November 23 and was preceded for two weeks by pain in the left lower abdomen. At this time there was a dark bloody flow having a foul odor for eight days, followed by "spotting" until December 8, when a regular or normal period began and lasted five days. On December 18, she noticed nausea and pain in the left lower abdomen, both of which lasted about one month. There has been no subsequent bleeding.

An examination April 18, 1938, revealed marked enlargement of the breasts and an intrauterine pregnancy with the fundus 22 cm. above the symphysis pubis. Fetal movements were palpable.



Fig. 2.—Follicle type of granulosa cell tumor.

Unfortunately, I have no hormone determinations in this case, but for this reason, I have given the detailed calendar history. An attempt will be made to correlate the clinical features of the case with the existing pathology.

Why should the above patient have had periods of amenorrhea for nine years, followed by a more frequent symptom, irregular and excessive menstruation?

Schulze⁶ describes the case of a woman twenty-seven years of age with a five-year sterility, who had always menstruated profusely and regularly until the two years previous to operation, during which the menses occurred every one or two months and were scanty. Two years after a left salpingo-oophorectomy because of a granulosa cell tumor, the patient gave birth to a full-term child.

The fact that a pregnancy occurred within three months after marriage or six months after operation, proves, at least in the above described case, that there is a rapid return to normal of the hormonal and reproductive system, following removal of the granulosa tumor. There is every possibility that sterility should occur in the presence of this tumor because of the marked hyperplasia of the endometrium and lack of ovulation. The absence of follicles and corpora lutea in the ovaries substantiates this view.

tent, worse on the days when there was only a scant flow, but never severe enough to confine her to bed. The vaginal bleeding had continued daily for the past four months with a progressive increase in pain. The patient contemplates marriage as soon as her health will permit.

Physical examination revealed a white female, weighing 140 pounds, with the normal distribution of fat. The breasts were slightly larger and more pendulous than one would expect. The distribution of hair was normal. There was a moderate secondary anemia. Vaginal examination showed a nulliparous introitus and healthy cervix. The uterus was freely movable, of normal consistency, and was enlarged to the size of a six weeks' pregnancy. The right ovary was prolapsed, enlarged, and movable.

With a preoperative diagnosis of endometrial hyperplasia and cystic right ovary, the patient was operated upon May 11, 1937. A dilatation and curettage produced a large amount of endometrial tissue, grossly hyperplastic. A midline abdominal



Fig. 1.—Typical hyperplasia of endometrium.

incision was made and the uterus was found to be enlarged. The right ovary was completely replaced by a tumor measuring 4 by 3 by 3 cm., and lay free to the right of the cul-de-sac. The left ovary appeared grossly normal, and there were no follicles or evidences of recent corpora lutea. Since there was no apparent peritoneal or lymphatic involvement, and the growth was grossly a well-encapsulated granulosa cell tumor, right salpingo-oophorectomy and appendectomy were performed. Cut section of the tumor showed a solid, grayish pink, granular mass divided by numerous trabeculae. It resembled somewhat a section of hob-nail liver. Microscopic examination proved this to be a folliculoma type of granulosa cell tumor. The patient was discharged on the twelfth postoperative day, after an uneventful recovery.

Several days later the patient had "soreness" in the lower abdomen and temperature ranging from 99° to 102° F., which lasted for two weeks or until the onset of menstruation on June 11. The flow was profuse for eight days, requiring bed rest, and accompanied by slight "cramps" the first two days. "Vaginal bleeding" continued as before the operation until July 1 when her physician was

STATUS OF THE THECOMA AND ITS RELATIONSHIP TO THE GRANULOSA CELL TUMOR

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THE incretory tumors of the ovary have in the past decade come much to the fore. The granulosa cell tumors as are now well established, present many vagaries of morphology, ranging from the immature fibromatoid to the mature folliculoid type. From this group a new entity has been segregated. In 1932 a series of cases of lipid-containing tumors, desmoid in nature, with more or less marked degree of luteinlike transformation of the cells was reported by Löffler and Priesel as cases of "fibroma thecocellulare xanthomatodes ovarii." In 1934 these authors reported four more such cases.¹ This suggestion has been accepted in Europe by Schiller, Brosig, and others. In this country Melnick and Kanter² reported two similar cases and Geist³ reported 5 such cases. This type of tumor is now commonly referred to as "thecoma."

In marked disagreement with this new concept are many gynecologic pathologists. Strongly opposed to the segregation of these tumors are Novak and Gray,⁴ who draw attention to the fact that both the granulosa cell and the theca cell have a common origin from the embryonic ovarian mesenchyme. From the further fact that the biologic properties of these tumors seem to be similar, these authors see no reason for distinguishing this small "thecoma" group from the granulosa cell tumors. It was suggested by Novak that it might be more appropriate to designate this whole group as "progranulosa cell" tumors.

The purpose of this paper is not to try to settle this problem but to present an interesting case in which there are neoplastic elements markedly resembling both granulosa and theca cells. This case has been reviewed by Schiller, who believes it to be an unusual case of combined thecoma and granulosa cell tumor.

CASE REPORT

Mrs. I. W. (c10486), a white female, aged 59 years, mother of four children, was admitted to the Michael Reese Hospital on July 16, 1936. She complained of sudden onset of uterine bleeding which was pseudomenstrual in type, after having experienced her climacteric ten years previously. Three months before being seen by one of us (J. P. G.) she first noted vaginal bleeding which simulated in every way a menstrual period except that it lasted three weeks. Since then she had several short periods of bleeding which ceased, only to return after a free interval. The last flow of blood ended two days prior to operation. The breasts were large and pendulous. Pelvic examination revealed an enlarged, soft uterus one and one-half times the normal size and a tumor of the right ovary about 4 cm. in diameter. The preoperative diagnosis was granulosa cell tumor. A quantitative estrin determination of the urine on admission to the hospital, unfortunately was omitted. A supracervical hysterectomy and a bilateral salpingo-oophorectomy were done. The patient made an uneventful recovery.

Examination of Specimen.—*Gross:* The specimen consisted of the supracervical portion of the uterus with tubes and ovaries attached. The excised portion of the uterus measured 4 cm. in width across the fundus and 5 cm. in length. The myometrium was uniformly soft. The endometrium was very redundant and polypoid. The right ovary was firm, enlarged and measured roughly 4 by 4 by 3 cm. The external surface was nodular and focally hemorrhagic. Sectioned surface of this ovary revealed a lobulated, glistening, brownish yellow to gray mass which was mottled by yellowish dots. This mass occupied the greater part of the ovary and

CONCLUSIONS

Though it is clinical conjecture, these cases of pregnancy suggest that (1) large doses of estrin over long periods of time would have no permanent ill effects on the reproductive system. (2) By controlling endometrial hyperplasia with luteinizing hormones and assisting ovulation, pregnancy is more likely to take place.

In those cases in which an endometrial study has been made (Fig. 1), a cystic type or hyperplasia is almost invariably found. If it is possible to assume that a hyperestrinism existed for ten years, then the periods of amenorrhea can be explained, for it has been shown that there is a fall in level of estrin just prior to the onset of menstruation; an estrin secreting tumor would prevent this normal cyclic drop. In an uncomplicated endometrial hyperplasia, there are frequently periods of amenorrhea, though there may be a surprising regularity of menstruation, if indeed it can be called such. Novak⁷ refers to the bleeding associated with hyperplasia as "anovulatory menstruation," or periodic bleeding without ovulation. This is not a true menstruation, but rather hemorrhage from pin point areas of necrosis.

There are recorded in the literature two cases of pregnancy occurring after the removal of granulosa cell tumors and several others associated with sterility. Klasten's⁵ patient had never menstruated at the age of 29 years, at which time the tumor was removed. Regular menstruation began after one year and the patient gave birth to one child. Ten years elapsed and a period of three years' amenorrhea preceded a second operation, when a retroperitoneal tumor of the same granulosa type was removed.

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Vayssiére: Etiology and Medical Treatment of Pruritus Vulvae, Gynec. et obst. 36: 209, 1937.

For immediate relief, the author advises cold baths of short duration, with careful drying. Among the etiologic factors he mentions urinary infections, oxyuria, trichomonas, diabetes, pelvic cellulitis, fibroids, salpingitis, albuminuria and endocrine disturbances.

During pregnancy, pruritus is usually due to mycosis, trichomonas or bacterial infection. Treatment must be directed against these organisms. In cases due to an endocrine disturbance, administration of estrogenic substance is the treatment of choice.

in contrast with the abundant lipoid accumulation taking place in the surrounding theca interna. The lipoids as demonstrated by sudan III were in the form of cytoplasmic granules or fine droplets. When studied with the polarizing microscope, there was found among the lipoids an abundance of doubly refractile crystals, i.e., cholesterol and cholesterol esters.

Microscopic study of sections of the endometrium exhibited cystic and glandular hyperplasia.

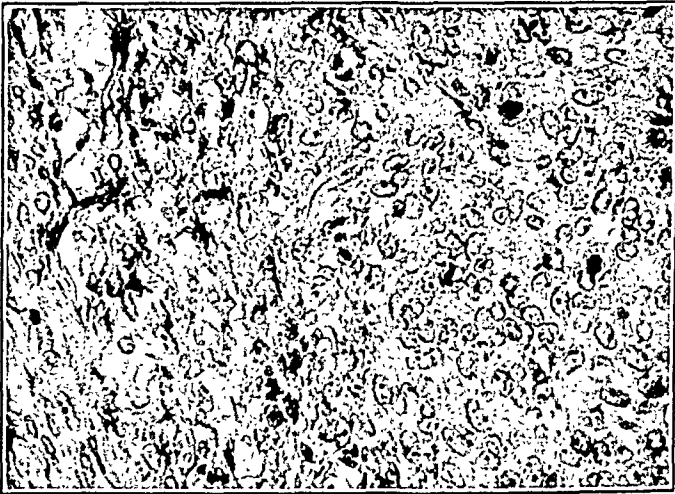


Fig. 2.—A focal mass of large pale luteinlike cells surrounded by fibrous tissue.



Fig. 3.—Note the striking sudanophilic reaction which photographs black in the fibromatoid tissue surrounding a focal mass of feebly luteinized epithelioid granulosa cells (upper left). The fibromatoid tissue (lower right) not in immediate juxtaposition to those cells show but scattered masses of lipoid droplets and meager luteinization.

DISCUSSION

A critical study of this case lends further support to the theory that both the theca and granulosa cells have a common origin from the ovarian mesenchyme. It is thought that the granulosa cells of the developing follicle stimulate the adjacent

measured 3.5 by 2.5 cm. At one border of the mass a firm grayish-white glistening nodule 1 cm. in diameter was present. The left ovary was atrophic. The tubes showed some evidence of fibrosis.

Histologic study of sections from the right ovary revealed that the neoplasm was circumscribed by a shell of compressed ovarian stroma. The main component cell of the neoplasm was polyhedral in shape and had a moderate-sized hyperchromatic nucleus. Mitotic figures were occasionally seen. The cytoplasm was faintly stained, finely granular, and frequently vacuolated. The cell membrane was poorly defined. The cellular arrangement formed a diffuse anastomosing trabecular network grouped about myriad sinusoids and large capillary spaces. In certain areas there was a gradual transition from this anastomosing trabecular network to a more compact cellular tissue (Fig. 1). Frequently this change was rather abrupt. Here interweaving bundles of fusiform cells with well-stained elongated nuclei gave the appearance of a distinctly cellular fibroma. From these areas thick fasciculi of the cellular fibromatous tissue traversed the neoplasm irregularly lobulating it. Frequently focal masses of epithelioid cells were festooned by fibrillar fibrous tissue or by broad fibromatous sheafs of plump fusiform cells. In certain of these focal areas the cells were quite

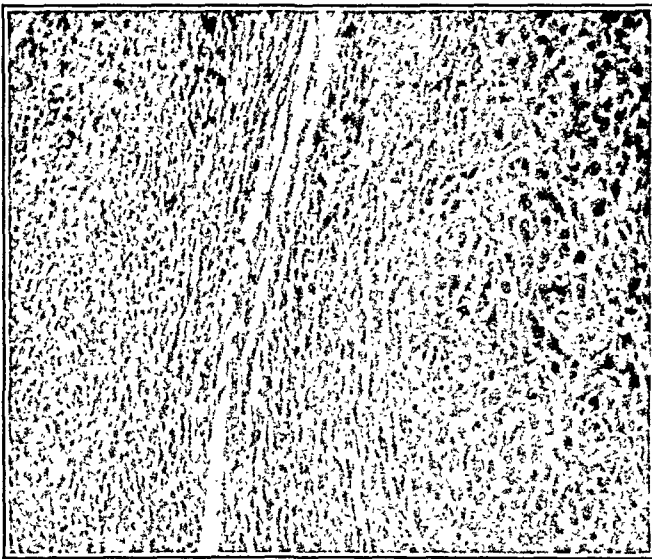


Fig. 1.—Zone of transition between a fibromatoid type of tissue (left) and an anastomosing trabecular type of epithelioid tissue (right).

large, pale staining, and epithelioid in character. The nuclei were large, oval and vesicular with well defined nucleoli. The cytoplasm was abundant and spongy. These cells had a marked semblance to lutein-like cells (Fig. 2).

The remarkable points of interest in the study of this tumor were brought out only when fat stains were undertaken. The constituent cell in the loose trabecular areas varied in its lipochromic content from scanty to moderate. In other areas the lipid content of these cells was greater; moreover the interlobular strands of fibromatous tissue in these zones were remarkably rich in sudanophilic droplets. Wherever the fibromatous tissue was in juxtaposition with masses of granulosa cells the lipid staining reaction of the former was greatly intensified. Surprising was the observation that in the solid masses of fibromatous tissue, certain parts stained heavily with sudan III, while other immediately adjoining areas of this fibromatous tissue were more or less devoid of sudanophilic lipoids. Most interesting too, was the observation that some of the focal masses of granulosa cells which gave some semblance to luteinlike cells showed but meager lipid accumulation, while the fibromatoid stroma surrounding these focal masses gave a striking reaction to sudan III (Fig. 3). Such areas call to mind the normal maturing follicle, just prior to rupture, when the granulosa cells show as yet but minimal luteinization

the case of "folliculome lipidique" studied by Moulonguet, which was without doubt a luteinizing granulosa cell tumor, were also doubly refractile. In our own case an abundance of doubly refractile lipoids was also observed.

SUMMARY

An ovarian neoplasm is reported composed of broad sheafs of xanthofibromatous tissue interlobulating masses of granulosa cells of the diffuse trabecular type. The transition between the two types of tissue frequently was not sharply defined. Sudan III stains revealed that the granulosa cells exhibited meager to moderate pseudoluteinization. The fibromatoid tissue for the greater part showed intensive cytoplasmic accumulation of fine lipid droplets. Where the fibromatoid tissue surrounded focal masses of granulosa cells, the peri-epithelial sudanophilic reaction was greatest. This process is strikingly analogous to the maturing normal follicle prior to rupture, when only feeble luteinization of the granulosa cells is present in contrast to the abundant lipid deposition of the theca interna.

It is felt that the tumor herein reported provides sufficient evidence to bridge the gap between the "fibroma thecocellulare xanthomatodes ovarii" (thecoma) and the "folliculome lipidique" of Lecène, linking those tumors which exhibit similar biologic properties into one group originating from a common type cell of the ovarian mesenchyme, the programulosa cell.

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PRIMARY GIANT GRANULOSA CELL TUMOR OF RETROPERITONEAL ORIGIN WITH DEVELOPMENT INTO THE MESOSIGMOIDEUM

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TUMORS that take their origin in the organs and tissues back of the peritoneum are of infrequent occurrence. The most frequently occurring tumors are those of the kidneys, adrenal glands and the pancreas, and these originate above the umbilicus. Retroperitoneal tumors originating below the latter are rare, and a primary retroperitoneal tumor consisting of granulosa cells, therefore of ovarian tissue, and developing far away from the normal location of the ovary is even less frequently observed. For this reason the case in hands seems worth while reporting, especially as it was difficult to make the histologic diagnosis. In addition, the case may throw light on the genesis of granulosa cell tumors by reason of its inception far from the ovary and back of the peritoneum at a spot where once was the germinal cell tract (Keimbahn).

CASE REPORT

A woman, 51 years of age, presented herself two years ago, because of increasing girdle obesity which did not yield to rigid dieting. She had ceased menstruating and

undifferentiated but potential mesenchyme transforming it into theca interna. The theca interna is composed of fusiform cells which have definite connective tissue characteristics. Before maturation of the follicle, theca cells take on a distinct epithelioid appearance. After rupture of the follicle, lipid droplets accumulate in their cytoplasm. The theca cells are also active during the process of follicle atresia. Following degeneration of the ovum and of the granulosa cells, the theca cells proliferate, enlarge and accumulate lipid, a pseudoluteinization.

Both theca lutein cells and granulosa lutein cells contain lipoids. Granulosa cell tumors as a rule do not, to any marked extent, show lipid accumulation. It has long been recognized that some granulosa cell tumors undergo certain degrees of so-called luteinization. Klaften⁵ in classifying granulosa tumors included a "luteiniformis" variety. In 1910 and again in 1927 Lecène described an ovarian neoplasm rich in fat and lipoids which Moulouguet termed "folliculome lipidique."⁶ Plate⁷ in 1933 reported a third such case. A study of Plate's illustrations, which are in a measure a replica of Moulouguet's, convinces one of the granulosal nature of the tumor in spite of its richness in lipoids. In 1934 Novak and Brawner⁸ reported a large series of granulosal cell tumors. Their Case 28 resembles a spindle-cell sarcoma in which numerous bands and islands of luteinlike cells were found. Marked lipoidal changes were demonstrable by differential staining. They believed their case to be a granulosal cell tumor of the "folliculome lipidique" type.

Reports of so-called luteomas or lutein cell tumors appear in the literature from time to time. Those which are not hypernephroid ovarian neoplasms are probably nothing more than excessively luteinized granulosa cell tumors.* A rare exception indeed, however, is Pierre Masson's case of "epitheliome du corps jaune" illustrated in his book.⁹ The case reported by Wills and Romano¹⁰ in 1935 was found on further study by another gynecologic pathologist to be a hyperluteinized granulosa cell tumor.

The term luteinization should be used with caution. The endometrium very accurately mirrors the endocrinopathies of the ovary. The word luteinization when applied to granulosa cell tumors, should be reserved for those cases in which the endometrium shows premenstrual or gravid changes. Luteinization and excessive cellular lipid accumulation are not synonymous. By far the greater number of cases referred to in the literature as luteinized granulosa cell tumors because of their abundant lipid content, exhibited glandulocystic hyperplasia of the endometrium. This is characteristic of excessive estrogenic stimulation and not of luteinization. Perhaps the term pseudoluteinization is a better one for the cases in which the endometrium is hyperplastic, but not in the secretory phase.

CONCLUSIONS

With the evidence at hand, it is apparent that pseudoluteinization is not the distinctive feature of thecomas alone. Furthermore the purely fibromatoid character of thecomas is not a feature peculiar to such tumors, but is also seen in the immature, homogeneous type of granulosa cell tumor. It is now fairly well established that in the embryologic development of the ovary, granulosa cells are formed in loco from ovarian mesenchyme, from which likewise is formed the thecal and stromal tissue of the ovary. Since these cells have the potentiality of forming granulosa cells, which, however, have missed contact with the ovulum, they may, in developing, exhibit their inherent congenital and constitutional tendencies. In so doing, they may exhibit every step from the fibromatoid to immature trabecular formations to cordlike structures, and also to simulate follicle formation. This explains the great variation in histologic descriptions reported in the literature ranging from sarcomatous to carcinomatous changes.

Polariscopic examination of the lipoids in thecomas reveals that they are for the greater part doubly refractile, i.e., cholesterol and cholesterol esters. The lipoids in

*Since writing this paper Traut and Butterworth have published an excellent study in the AM. J. OBST. & GYNEC. 84: 987, 1937, in which they show that experimentally produced granulosa cell tumors in the mouse ovaries frequently resemble lutein tumors.

and wandering cells (histiocytes) and a poorly stained secretion. Other areas show masses of cells of the same type, irregularly arranged. The vessels (capillaries) contain many polymorphonucleated cells. The connective tissue is poorly developed, but follows the epithelial cells throughout the entire tumor.



Fig. 1.—Cross section of tumor showing spongiolike tissue.

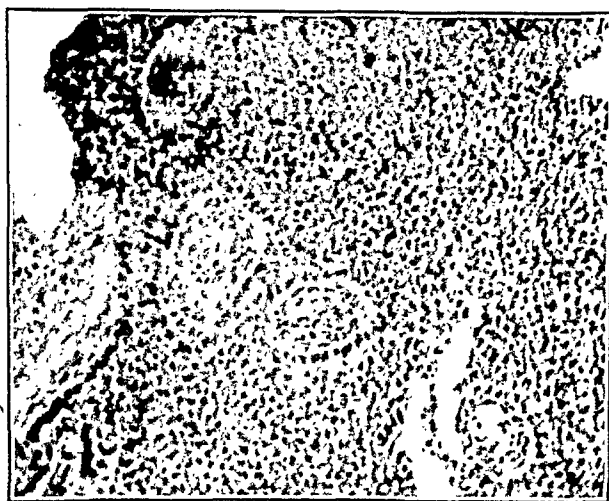


Fig. 2.—Part of tumor with follicle-like arrangement. (Magn. 170 diam.)

The tumor is evidently of embryonic origin, its cells well differentiated (i.e., not of an immature type, but embryonic). The origin of the tumor is probably the ovary. The tubular arrangement of the cells resembles the arrangement of the cells of Pflüger's tubuli (Pflüger's Schläuche). There are no follicles present in the entire slide.

thought that this might be the cause of the gain in weight. Three years previously she had had a supravaginal hysterectomy because of numerous large myomas. At the time, apart from the myomatous uterus macroscopically there appeared nothing pathologic about the ovaries or the surrounding pelvic region. On examination there was a tumescence affecting the entire abdomen and extending upward under the costal arch. It looked like a pregnancy in the ninth month. The consistency of the tumor was firm-soft, with indistinct fluctuation. Pregnancy was out of the question because of the previous hysterectomy. On the other hand, it could have been a myoma arising at the point of amputation, but the small pelvis was free of tumor except for the extension of the large mass. No connection with the cervical stump could be shown. The possibility of an ovarian tumor was excluded inasmuch as both ovaries could be recognized by touch as little atrophied bodies. By elimination, therefore, a mesenteric cyst was diagnosed, with some likelihood of a softened myoma.

An attempt was made to establish intra- or retroperitoneal origin. Hesse's symptom is supposed to be of value in such cases, namely, a difference of some degree in the skin temperature of both legs. The symptom is ascribed to the pressure on the sympathicus. It is claimed that tumorous growths too small to be palpated have been discovered through this symptom. In this case, however, Hesse's symptom was not present, either because it is a first symptom which, in this case, had disappeared with gradual adaptation to the pressure from the tumor, or because the tumor, soft as it was, had projected itself into the abdominal cavity without exerting appreciable pressure on the sympathicus. The patient demurred at an x-ray examination because of the cost, so the operation was performed under the diagnosis of a mesenteric cyst or a softened myoma.

On opening the abdominal cavity, which showed no ascites, an enormous tumor was disclosed. It filled the entire abdominal cavity and had forced the intestines upward; only after further section of the cavity could it be moved, and then it was possible to establish that the tumor lay in the mesosigmoideum. The mesosigmoideum was divided in the direction of its vessels and the tumor was carefully isolated without opening a blood vessel. As the size made it unwieldy and the tumor itself fluctuated to touch, it was punctured and 3,500 c.c. of bloody serous fluid were drawn off. The tumor was still further separated, and it became evident that it originated on the left of the spinal column about where the ureter and the large vessels cross each other. It had developed toward the front into the abdominal cavity between the two layers of the mesosigmoideum.

The monster tumor was covered with a smooth capsule of connective tissue, which was nowhere perforated. In some places it was 1.5 cm. thick and coarse, in others it was as thin as a spiderweb and tore easily. The interior was of sponge-like tissue, which radiated from the periphery toward the center and was interspersed with cavities varying from the size of a cherry to that of a hen's egg. The center was a large cavity and like the smaller cavities it was filled with a bloody serous fluid. Extensions of the tumorous tissues projected themselves into this cavity like the fingers of a polyp, and floated about there freely (Fig. 1).

The pathologic diagnosis based on a frozen section was "medullary carcinoma of the mesentery, probably metastatic." This diagnosis was not entirely convincing. First of all, there was nothing like a perforated capsule. Then, too, there was the striking presence in the section of such areas, as in Fig. 2, where in the midst of solid tumor tissue there were visible areas showing an alveolar structure. The rounded oval mass of cells in the center was surrounded by a palisade-like layer of cells. At other places there was a tendency to form "follicle-like" cavities. All this roused the suspicion that there might be here a case of granulosa cell tumor. A microscopic section was, therefore, sent to the pathologist of Loyola University Medical School. The following was the diagnosis:

"The microscopic slide reveals a tumor consisting of small epithelial cells of equal size, with distinct nuclei, all of them equally stained, of equal size and shape. The cells are arranged in strands forming tubuli, which on longitudinal as well as transverse section, consist of many layers of cells. The cells are of cuboidal shape, their nuclei somewhat spindle-shaped. The lumina of the tubuli contain fibroblasts

ever, there were mild hemorrhages of brief duration at irregular intervals on account of proliferation of the uterine mucosa and subsequent necrosis. The fluid extracted from the tumor contained folliculin as proved by the biologic test. Such tumors apparently speak for the mesenchymal origin of the granulosa cell. They seem to be a lower state of development and seem to change into epithelial forms later.

A transformation of epithelial forms of growth into growth of connective tissue is not very plausible. Embryologic research has moreover shown that epithelial formations can proceed from the mesoderm. In granulosa cell tumors there are transitional forms which belong neither to the epithelium nor to the connective tissue (Fig. 3). The tissue of the granulosa cell tumor as well as the connective tissue are thus in relation with each other by means of intermediate forms which gradually and uninterruptedly keep changing to one another.

The case described is evidently that of a granulosa cell tumor which developed at an unusual point of the germinal cell tract (Keimbahn) far away from the ovary, and in the case of a climacteric woman in whom ova capable of maturing are no longer present and consequently no granulosa cells are formed. It would be interest-



Fig. 3.—Tumor with granulosa cells, connective tissue, and transitional cell forms between the two.

ing to pursue the point as to what was the solvent stimulus which in the case of this woman caused tissues at one point of the germinal cell road to turn to granulosa and develop tumor fashion. It is known that estrin (folliculin) has an antagonistic effect upon the gonad-stimulating hormone of the anterior pituitary, and that after the ovaries ceased functioning there is an overproduction of the pituitary hormone. This could not influence the functionless ovaries but could stimulate immature cells of the germinal cell road to transform into granulosa and develop tumor fashion.

SUMMARY AND CONCLUSIONS

1. The case presented is a granulosa cell tumor as shown microscopically and biologically.
2. It developed far from the functionless ovaries as a primary tumor.
3. This seems to support the opinion of Nussbaum, Boveri, Beard and others of the independent development of germ cells and somatic cells and their migration via the "Keimbahn" to the place where the sex glands develop.

Tentative Diagnosis.—Embryonic ovarian tumor, not malignant, probably originating from Pflüger's tubuli or granulosa cells of the ovary.

Meantime mice were being treated with the fluid contents of the tumor. The animals injected with the unfiltered fluid all died, evidently owing to the human blood content. Treatment with the filtered fluid caused in immature mice enlargement of the uterus which is peculiar to folliculin.

A section was sent to Dr. Walter Schiller who replied: "The tumor is a typical granulosa cell tumor, ripe, no indication whatever of malignancy."

The question arises, what justifies the diagnosis of a granulosa cell tumor? As in the case of all tumors, the presumption is that the tumor preserves to a degree the form, arrangement, and functioning of the mother tissue. Small tumors afford the best prospect of being recognized as to origin and developmental progress. The huge mature tumor in this case would accordingly be a less fit object lesson. Nevertheless it affords clues enough for the diagnosis.

Among the characteristics of granulosa cell there is their follicle-like arrangement, their tendency to form roundish cavities bounded by bands of cells. The tendency to this disposition can be noticed at many places in the tumor under discussion. In addition, there is the formation of Call-Exner corpuscles, characteristic mark of follicular epithelium. These corpuscles were at first thought to be newly formed ova, but later Thomsen showed that this formation is an hydropical swelling of granulosa cells, the remains of which are at first still in evidence but later liquefy, leaving an open lumen. The process is the same as with the formation of the follicular cavity. It is a physiologic process and serves to produce the liquor folliculi. At first the cells grow around the gap that takes shape without a change in their arrangement. It appears to be a reaction peculiar to granulosa cells that they grow rosette-wise about a large cell. This reaction must evidently be traced to the relation between egg cell and granulosa. It seems to result also in individual swollen granulosa cells, and to be retained also with tumor growth.

The granulosa cell tumors have a place of their own partly showing up a readily discernible connection with the normal granulosa and partly displaying no resemblance at all with normal ovarian cells. There is no uniform theory as to the derivation of these tumors. The tumor in the case under discussion deserves special attention on account of its atypical point of origin so far away from the ovary, thus apparently bearing out Fischel's contention that the granulosa is derived from the mesenchyma. Granulosa cell tumors often present connective textural forms of growth which remind one of fibromas or sarcomas. This seems to speak for their mesenchymal origin. According to Pflüger, Waldeyer and Hertwig the granulosa cells are derivatives of the germinal epithelium (the epithelium of the plica genitalis). But thus it cannot be explained how granulosa cell tumors can originate in the ovary of women after the menopause or, as in this case, far from the ovary as a primary tumor. All the difficulties in explaining the histology of granulosa cell tumors are solved by the research work of Fischel, who proves that the granulosa cell originates in the mesenchyma through differentiation called forth by the formative stimulus of the primitive sexual cells after the latter have made their distant migration to the spot. According to Nussbaum, Galton, Boveri, and Beard the sexual cells follow a course of development which differs altogether from that of the other somatic cells, and they retain the totipotency which is essential to the first offshoots of the fertilized ovum. So the primitive sexual cells (archygonocytes) are the mother cells of sperm cell and ovum. The latter are not the derivatives of the fertilized egg.

In Fischel's opinion there occurs no mutual intergrowth of germinal epithelial cells and the underlying embryonic connective tissue. But the connective tissue cells directly under the germinal epithelium begin to multiply more vigorously than the others. What was styled "epithelial core" before is as a fact a "mesenchymal core." Primary sex cells (archygonocytes) are found scattered about in this mass. The formation of the plica genitalis out of the coelom epithelium and the mesenchyma never begins until the primitive sex cells have penetrated to these sections. Sometimes the granulosa cell tumors show purely connective textural forms of growth, thus presenting appearances of fibromas or sarcomas. The author is in possession of a fibromatous ovarian tumor which had caused an enlargement of the uterus, so that the patient thought she was pregnant. At the same time, how-

The third procedure is marsupialization; that is, the thickest edges of the membranes are sutured to the margins of the incision, and the cavity is packed and drained. The placenta separates bit by bit. This method is imperative if infection is present or imminent; it has the added advantage of facilitating the control of hemorrhage by packing if placental separation occurs.

Eisaman and Ziegler's⁵ patient had a bilobate placenta. The upper lobe, connected by a narrow isthmus of tissue to the lower lobe only, was removed. The lower lobe was the larger, and the cord was attached to it; it was adherent to "the posterior surface of the uterus and broad ligament and to the right wall of the pelvis." It was left in situ and the abdomen closed without drainage. After two weeks, sepsis set in; drainage from the wound lasted for several days. Both mother

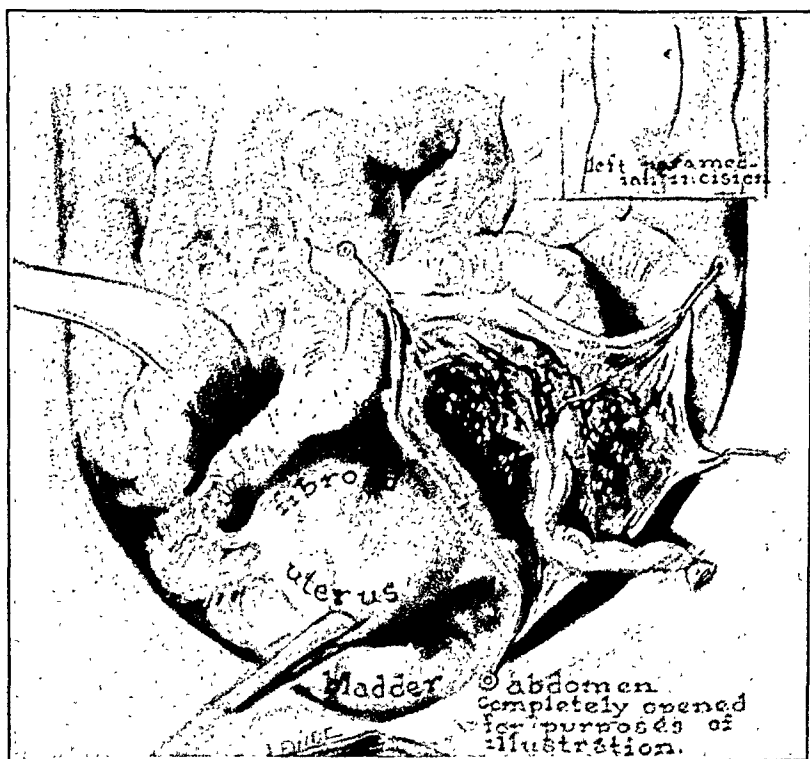


Fig. 1.—Case 1. Left paramedian incision. Abdomen opened in drawing for purposes of illustration so that fibroids and position of placenta and membranes can be seen. Intestines are distended.

and child survived. Best⁶ employed marsupialization in an emergency operation following abdominal hemorrhage at about four months. The mother was discharged in forty-nine days, after a stormy convalescence. Autopsy in a previous case of the present author's⁷ showed the placenta so firmly adherent to the intestines, left ovary, mesentery, and left broad ligament that removal would have been impossible.

REPORT OF CASES

CASE 1.—J. B. (Harlem Hospital No. 59832), a 23-year-old colored housewife, para ii, gravida iii, was admitted to the Harlem Hospital Sept. 5, 1935, at noon. Family and personal histories were of no interest, except for one induced abortion at four months. The patient's last menstrual period began Oct. 17, 1934; the expected date of confinement was July 24, 1935. Pregnancy had proceeded uneventfully. No life had been felt for the past two months. Three weeks before admission, slight vaginal bleeding was noticed. Pains began at 2:00 A.M., ten hours before admission; the

4. It seems probable that some of the germ cells (archygonocytes) remain at some place in the germ cell road and give cause to tumor formation.

5. The stimulating agent in this case was perhaps overproduction of pituitary hormone after the ovaries lost their antagonistic effect upon the anterior pituitary.

6. This case seems to support Fischel's mesenchymal theory of the granulosa cell, since the connective tissue can assume very different forms and may have developed into granulosa under the influence of arrested germinal cells and pituitary hormone.

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6633 SHERIDAN ROAD

THE TREATMENT OF LATE ABDOMINAL PREGNANCY*

WITH REPORT OF TWO CASES

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THERE is no single answer to the question, "What is the therapy of extrauterine gestation?" Treatment depends on a number of factors, such as the viability of the fetus, the time of diagnosis (whether preoperative or operative), the presence of complications, and the laparotomy findings.

As to the time of operation, Beck¹ states: "Laparotomy is indicated as soon as the diagnosis is made. If, in the interests of the child, it is desirable to postpone operation, the latter should be done about two weeks before term." According to Titus,² the thirty-sixth week is the optimal time for operation if saving the child is the primary consideration. He adds that, if fetal death is discovered, some authors prefer to defer operation for a week or so, believing that thrombosis of the placental blood vessels will lessen hemorrhage. Anspach³ advocates waiting six or eight weeks. Hellman and Simon,⁴ in their review of the literature, discredit the waiting policy because of the maceration and sepsis likely to follow fetal death and placental separation.

At operation, the chief problem is the management of the placenta. It should be handled as little as possible until the child has been delivered. There are then three courses of action: First, it *must* be removed if the site of its implantation permits. Second, if, because of its adherence to vital structures, the placenta cannot be disturbed, it may be left for absorption, and the abdomen closed without drainage.

*Read before the Section of Obstetrics and Gynecology of the New York Academy of Medicine on October 26, 1937.

ovary, left tube, left round ligament, and mesentery of the small intestine, marsupialization was deemed advisable. The umbilical cord was ligated and cut as deeply as possible. The membranes of the sac were loosely approximated and sewn to the edges of the abdominal incision. The cavity was packed with iodoform gauze, and a Penrose drain was inserted in the lower angle. The operative wound was closed with interrupted silk sutures and dressed; a tight abdominal binder was then applied. The patient's condition was good on her return to the ward. The operative technique is illustrated in Figs. 1 to 3.

The abdominal wound drained for about three weeks after operation. The iodoform gauze was changed every two days, less packing being used each time. Because of marked anemia (hemoglobin 45 per cent, red blood corpuscles 1,520,000),

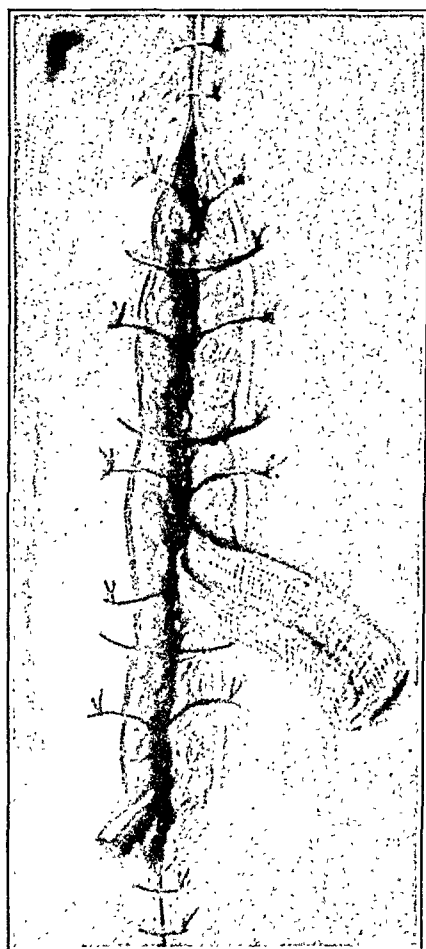


Fig. 3.—Case 1. Closure of incision. Part of gauze drain remaining outside, and at lower tip of incision a small Penrose drain is inserted into the skin, fat, and muscles.

a transfusion of 350 c.c. of citrated blood was administered on September 21, the fifteenth postoperative day. Sloughing of the placenta commenced the same day and continued for thirty-one days, until October 22. The patient was allowed out of bed on the second of November, the fifty-seventh postoperative day, and was discharged as improved on Nov. 25, 1935, the seventy-ninth day. Convalescence had proceeded uneventfully, except for anemia, and for a possible phlebitis during the first week of October. When seen again in April, 1936, the patient had no complaints.

CASE 2.—H. J. (Harlem Hospital No. 62089), a 27-year-old colored housewife, para 0, gravida i, was brought by ambulance to the Harlem Hospital at 7:15 p.m. on Nov. 26, 1935. She had had an appendectomy at the age of eleven, and a left

interval was thirty minutes at onset and from fifteen to thirty minutes at admission. Bleeding was more marked than previously.

On examination, the patient's physical condition appeared good. The abdomen was the size of a full-term pregnancy with a small baby. No contractions were felt. The fetal parts could not be distinguished, and the fetal heart was not heard. There was a round mass, 6 by 6 cm., of moderately soft consistency, just above and to the right of the symphysis pubis; this was apparently attached to the uterus. Vaginal examination revealed moderate bleeding, with clots. The external os admitted two fingers; the internal os, one. No membranes or presenting parts were felt. There was a mass in the posterior cul-de-sac which felt like a fibroid.



Fig. 2.—Case 1.—Illustration showing placenta marsupialized to abdominal wall. Membrane is thickened, and sutures are taken through the membranes, peritoneum, abdominal muscles, fat, and skin. Large gauze drain placed in placental tissue. In this instance less of the drain is shown than is actually used, for purposes of illustration. Incision here extends from the symphysis to the xiphoid process.

Diagnosis of abdominal pregnancy was made. This diagnosis was confirmed roentgenologically the following day; moreover, the overlapping of the sutures indicated fetal death.

Operation was performed on September 6 as soon as the diagnosis had been confirmed by roentgenogram. The abdomen was opened by a left paramedian incision. A bluish purplish sac was seen; this appeared to consist partly of membranes and partly of placenta. After the cloudy contents of the sac had been aspirated through a stab wound, the opening was enlarged and a macerated male fetus weighing 5 pounds, 4 ounces was extracted. The uterus was found enlarged to the size of a six weeks' pregnancy, with a fibroid on the posterior wall. Because of the cloudiness of the fluid, the maceration of the fetus, and the attachment of the placenta to the left

ENDOMETRIAL HYPERPLASIA (PUBERTY), ADENOCARCINOMA, FIFTEEN YEARS' FOLLOW-UP*

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THE question as to whether hyperplasia of the endometrium should be regarded as a precancerous lesion is still open for much discussion. Ewing writes: "In a series of cases of hypertrophic endometritis every gradation may be observed from normal glands to those of adenoma malignum." Taylor in 1932, after a study of adenocarcinoma cases, showed evidence that hyperplasia of the endometrium may be a predisposing factor in the later development of cancer. In this study, hyperplasia of the endometrium was found in cases of adenocarcinoma far beyond the menopause. Novak emphasized the fact that ordinary hyperplasia of the reproductive epoch is not only frankly benign from the histologic standpoint but also that it has no apparent predisposing influence in the causation of adenocarcinoma during menstrual life. Nevertheless, he found that postmenopausal hyperplasia was also associated with adenocarcinoma later in the menopause. The following case of endometrial hyperplasia with subsequent development of adenocarcinoma is reported in a girl eighteen years of age.

H. I., 18 years of age. (Hospital No. 6467.) First admission on Dec. 7, 1923. *Chief complaint:* Profuse menstruation. Mother and father died of tuberculosis. Patient had measles as a child. Had been a patient at a tuberculosis sanitarium for almost one year. *Menstrual history and present illness:* She began to menstruate at the age of fifteen years. Period was established with ease; normal, five day type. She had no dysmenorrhea and was never incapacitated. Periods were regular until 1922 when she went swimming during her menstrual period. This period lasted two weeks. It was profuse, with numerous clots. She then began to menstruate profusely every two weeks until about six weeks prior to admission when she began to flow and continued until the date of admission. During this period, she lost weight and became weaker. Examination revealed an acutely ill young female showing evidence of a marked secondary anemia and loss of weight. The lungs showed evidence of moderately advanced tuberculosis. The heart was grossly negative. Rectal: Cervix was small and posterior; uterus anterior, normal in size, shape and consistency and insensitive to motion. Adnexa and parametria were grossly negative. *Laboratory data:* Blood: R.B.C. 1,972,000; W.B.C. 8,800; polymorphonuclears 58 per cent; lymphocytes 42 per cent; Hg. 60 per cent. Urine: Negative. Blood pressure: 105/55. Sputum: Positive for acid-fast bacilli in large numbers. Operation: Dilatation and curettage, insertion of radium 50 mg. for eight hours. Gross findings: Uterus normal in size and position. Curettings considerable in amount. Microscopic: Endometrial hyperplasia (Fig. 1).

Second admission on Aug. 19, 1924. *Interval history:* After leaving the hospital patient was improved for one month. The bleeding had stopped. The following month she had profuse vaginal bleeding which lasted for two weeks. During these bleeding spells, she became dizzy and very weak. After receiving conservative treatment for several months with no success, she was advised to return to the hospital. Examination revealed a grossly negative pelvis except for vaginal bleeding. The physical findings and laboratory data were similar to those on the previous admission. Operation consisted of curettage and insertion of 25 mg. of radium which remained for sixteen hours (400 mg. hr.). The gross findings revealed the uterus to be normal in size and position, and curettings moderate in amount. Microscopic: Endometrial hyperplasia.

*Read at a meeting of the New York Obstetrical Society, January 11, 1938.

salpingectomy at the age of eighteen. Menstruation, which began at eleven, was irregular. The last menstrual period was April 15, 1935; and the expected date of confinement, Jan. 22, 1936. Spotting occurred in June and July. The patient felt dizzy occasionally. She began to attend another clinic on November 3. When examined at this clinic on November 24, she was told that she was perfectly well. She became ill November 26. Pains in the epigastrium, radiating to the back, occurred at intervals of from ten to fifteen minutes. The patient became very restless, vomited, and suffered from severe cold sweats.

On admission, the patient was in profound shock. She was cyanotic and restless. Blood pressure was unobtainable. The pulse was rapid and thready, the skin cold and clammy. The pupils reacted sluggishly to light. The tongue was dry, and the breath had a foul odor. The heart rate was increased. The lungs were clear. There was evidence of marked loss of blood. There was generalized abdominal tenderness, but no rigidity. A mass in the abdomen extended to three fingers above the umbilicus. The fetal outline was indefinite, and the fetal heart was not heard. On rectal examination, the cervix appeared to be dilated one finger. No presenting part was felt in the cervix. Diagnosis was either premature separation of the placenta, or ruptured uterus of unknown etiology.

Operation was performed November 26, two hours after admission. A left paramedian incision was made. A moderate amount of fluid blood escaped when the peritoneum was opened; numerous blood clots were scattered through the abdominal cavity. The fetus, lying free in the peritoneal cavity, was easily delivered, together with placenta and membranes. The membranes were attached to what was apparently the right broad ligament. There was no tube on the left side. An ovary attached to the left cornu appeared to have a corpus luteum of pregnancy. The uterus was about the size of a three months' pregnancy. The abdomen was sutured in layers without drainage. During the operation, the patient received 1,000 c.c. of normal saline and 500 c.c. of citrated blood, to which she reacted well. She was returned to the ward in fair condition. She was then placed in the shock position and given morphine sulphate, hot blankets, and another infusion of 1,000 c.c. of normal salt solution.

The fetus was that of a premature female weighing 2 pounds, 13 ounces. Autopsy showed both lungs to be purple and atelectatic, and there was moderate congestion of the cerebral vessels. The placenta measured 20 by 10 by 1.5 cm. It was composed of two lobes, to the maternal surface of one of which a Fallopian tube was attached.

The abdominal wound healed by primary intention, except for a slight superficial infection, which developed on the thirteenth postoperative day. This was followed by a pelvic cellulitis on December 10, the fourteenth postoperative day. Convalescence otherwise progressed steadily, and the patient was discharged in good condition on Jan. 3, 1936, the thirty-seventh day after operation.

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50 mg. of radium for eight hours (400 mg. hr.) Gross findings showed uterus to be normal in size and curettings moderate in amount. Microscopic: Endometrial hyperplasia.

Fourth admission on Oct. 25, 1935. *Interval history:* For two months following the previous admission, the menstrual periods became irregular and less profuse. She then began to bleed profusely and passed large clots with the following menstrual period. In April, 1929, she received four roentgen ray treatments (300 r). The periods became irregular and the flow was scant until the latter part of 1932, when the periods became profuse and lasted from ten to twelve days. In February, 1933, the patient received two roentgen ray treatments (350 r). Bleeding diminished and the menses became irregular. This continued until the early part of 1935 when periods became profuse with passage of large clots and associated with pain. Painful menstruation was observed about one month prior to admission. Examination revealed a grossly negative pelvis. The uterus was curetted for diagnosis. Curettings were moderate in amount including a small endometrial polyp which was firm in consistency. Microscopic: Endometrial polyp with secondary adenocarcinoma (Fig. 2). The patient then received four roentgen ray treatments (600 r).

Fifth admission on Nov. 11, 1936. *Interval history:* Since discharge from the hospital, patient had no symptoms but returned for panhysterectomy. Examination revealed findings similar to previous admission. Panhysterectomy was done. Microscopic: Endometrial hyperplasia, adenomyosis, and endometrial polyp with secondary adenocarcinoma.

Since operation, the patient has been followed very carefully. She has increased in weight, feels perfectly well, and examination reveals a negative pelvis.

COMMENT

One of the most striking clinical observations in this case has been the persistence of vaginal bleeding after small repeated doses of radium and roentgen ray. The hyperplasia of endometrium has been marked. This seems to indicate that the amount of irradiation employed was not sufficient to control the factors involved in the stimulation of the endometrium and vaginal bleeding. Whether or not this is the result of excessive stimulation with estrin, it is very difficult to say. The question of repeated irradiation as a causative factor in the production of adenocarcinoma has been covered by reports of Fournier, Strachen and others who found that adenocarcinoma had existed prior to the irradiation for the supposed benign lesion.

SUMMARY

1. A case of endometrial hyperplasia with subsequent adenocarcinoma in a young girl is reported.
2. Persistent vaginal bleeding after irradiation should be thoroughly checked by repeated curettage and endometrial study.
3. Persistent hyperplasia of the endometrium after repeated irradiation should be closely followed.

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123 CLINTON STREET

DISCUSSION

DR. HOWARD C. TAYLOR, JR.—It is almost inconceivable that a carcinoma of the corpus could have as a precancerous lesion anything but a hyperplastic lesion of some type. The great question is whether we are always dealing with a single entity when we talk about endometrial hyperplasia. Ordinarily, when we use this term, we are

Third admission on Jan. 26, 1929. *Interval history:* Since patient left the hospital she had irregular menstrual periods but not profuse. There was no associated pain present. For about one year prior to admission, the flow again became more profuse. She was advised to return to the hospital. Examination revealed a grossly negative pelvis except for vaginal bleeding. The physical findings and laboratory data were similar to those on previous admission. She had curettage and insertion of



Fig. 1.—Hyperplastic endometritis in a girl 18 years of age after one year of profuse menstruation. ($\times 200$.)



Fig. 2.—Endometrial hyperplasia, adenocarcinoma after three doses of radium 400 mg. hr. (1923, 1924, 1929), and three doses of roentgen ray (300 r in 1929, 305 r in 1933, and 600 r in 1935). ($\times 200$.)

weak. Later her general condition improved and on December 17 another paracentesis was done, withdrawing two and one-half gallons of fluid. Her general condition improved so markedly that on Jan. 2, 1936, a laparotomy was performed. The incision was suprapubic, but above the umbilicus because of the distortion due to the heavy apron of fat. Two gallons of fluid were withdrawn from the large left ovarian cyst. The right ovary was the size of a large orange. Both ovaries were hurriedly removed and the abdomen closed. Her postoperative course was uneventful and she left the hospital Jan. 22, 1936, weighing 298 pounds.

The pathologic report was as follows: Multilocular pseudomucinous cystadenomas of ovaries (benign). (The right ovarian cyst measured 8 by 5½ by 2 cm. and the left ovarian cyst measured 23 by 8½ by 10 cm.)



Fig. 1.

Fig. 1.—Photograph, taken shortly after admission before a paracentesis, shows enormous distention of the abdomen and large apron of fat. Weight 409 pounds.

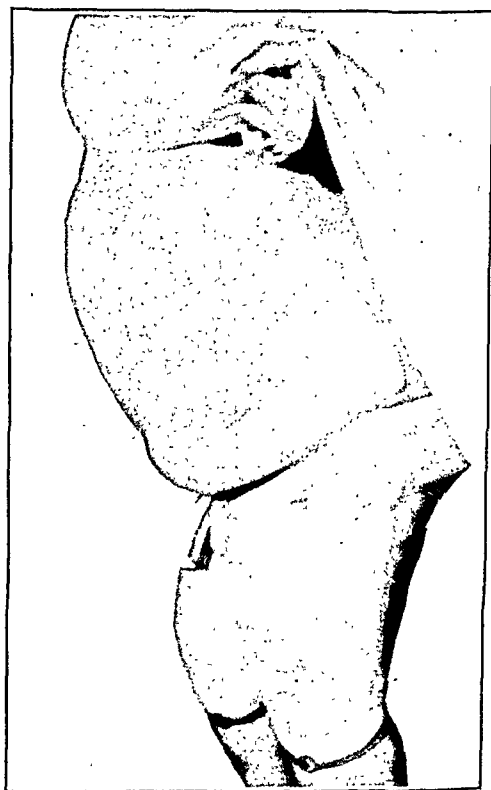


Fig. 2.

Fig. 2.—Taken Dec. 1, 1936, after removal of the ovarian cyst and lipectomy. She weighed 284 pounds at this time.

The patient improved satisfactorily at home, but was still handicapped by the large apron of fat. She was re-admitted to the hospital April 23, 1936, for a lipectomy. A fatty panniculus, weighing 19 pounds was removed. She left the hospital April 8, 1936, weighing 284 pounds.

The patient has been active and very well since the last operation. A month after her last dismissal she went to a "talkie" for the first time in her life.

Comment.—This patient had a pituitary type of obesity as well as an enormous ovarian cyst. She was in a critical condition on admission and therefore a gradual decompression of the tumor was required. We believe this conservative or guarded procedure was the chief factor in the final satisfactory results. Immediate removal of the cysts probably would have been fatal.

thinking of the hyperplasia of the menopause, or the years just before the menopause, which is associated with certain ovarian changes and possibly with a specific hormonal blood pattern. We certainly cannot say that carcinoma arises as a result of that specific type of hyperplasia. On the other hand it is probable that it arises on the basis of some local or diffuse hyperplastic changes, persisting in the menopause and perhaps developing on an entirely different basis from the classical hyperplasia.

DR. JAMES A. CORSCADEN.—Radium is an irritant, but irritants that we think of as causing carcinoma are persistent irritants. In other words, if we think of radiation as a stimulant of malignancy, we should think of it as a mild, persistent stimulant and not that which produces the acute destructive change that occurs after the application of 400 mg. hr. to any localized spot.

Statistically, the occurrence of carcinoma following radiation, irrespective of the cystic and glandular hyperplasia, is rare. We have about 1,500 cases of women treated by radiation and followed for an average period of seven and one-half years. There have occurred three cases of carcinoma of the corpus. This is probably a much smaller incidence than that among a like number of women, age for age.

AN UNUSUAL OVARIAN CYST

HARRY M. NELSON, M.D., DETROIT, MICH.

REFERENCES to large ovarian cysts are not uncommon in medical literature; however, reports of enormous tumors have become rather rare because of earlier surgical interference.

The case I am reporting is of interest because of the huge size of the patient as well as the tumor and because of the adaptation of the method of treatment for her particular requirements.

Mrs. M. H., aged 38 years, was admitted to Woman's Hospital Dec. 7, 1935, complaining of swelling of the abdomen, dyspnea, and palpitation.

The patient had been well as a child. Her menses started at the age of 14. They were regular and lasted five days, until five years ago when they became irregular and a little more profuse. The last menstrual period was November 20; it was rather profuse and lasted seven days.

She had had 7 full-term pregnancies, 5 children living and well. The sixth pregnancy terminated in a placenta previa. The baby died at birth and the patient had a hemorrhage at the time of delivery. The youngest child is six years of age.

There had been a steady increase in weight for the past ten years. Three years ago she noticed that her abdomen had increased in size. Since that time her activities became increasingly limited because of pressure and shortness of breath, particularly within the past five months. For the past two months she had been confined to bed. The patient believed that the swelling of her abdomen had increased fully a third in size in the last six weeks.

She entered another hospital for treatment early in November and was sent home after a week. It was felt that nothing could be done for her.

Examination on admission revealed an extremely obese white woman, acutely ill. Her weight was 409 pounds. Temperature 100° F.; pulse 120; respirations 30, rapid and shallow. Her pulse was irregular and weak. Her abdomen was tensely distended with a large cystic tumor mass. There was a large apron of fat which extended to the knees. Hemoglobin, 79 per cent; R.B.C., 4,020,000; W.B.C., 6,450. The urine showed a trace of albumin. Nonprotein nitrogen 37.1 mg. per 100 c.c. of blood.

On December 8 an abdominal paracentesis was performed and three gallons of clear yellowish fluid were removed. The patient's pulse became rapid and rather

upper quadrant and there appeared to be one engaged in the inlet to the pelvis. The vulva was greatly swollen as illustrated, and there was a clear serum oozing from a rupture of skin at the lower portion of the left labium majus. Blood pressure 170/120, temperature 101° F., pulse 100, urine albumin 4-plus, white blood count 28,150, hemoglobin 65 per cent.

Notwithstanding the toxemia several consultants agreed upon cesarean section as choice of procedure. A low cervical operation was completed in thirty-five minutes with patient under cyclopropane anesthesia and delivery of female double ovum twins. Convalescence was characterized by gangrenous slough of the skin and mucosa of the inner surfaces of both labia majora. Infection of the ulceration was the cause of some fever which ranged to 102° F. for a couple of weeks. A leucocytosis was noted of 30,000 (polymorphonuclear leucocytes 85 per cent). The toxemia was treated by intravenous magnesium sulphate, glucose and free fluids, and salt-free diet. There was some anemia (R. B. C. 3,100,000) and she received one transfusion.



Fig. 2.—Photograph of vulva three days after operation showing sloughing area on each labium majus.

The gangrenous ulceration responded to dry treatment with tannic acid powder and was almost entirely healed at end of twenty days in the hospital. The edema of vulva subsided in three or four days and that of the legs and feet at the end of ten days. The infants weighing 7 pounds, 3 ounces and 6 pounds, 5 ounces, respectively, at birth, nursed and did well and left the hospital with the mother on the twentieth day.

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GANGRENOUS VULVAR EDEMA NECESSITATING CESAREAN SECTION

RICHARD TORPIN, M.D., AND ROBERT BATTEY CRICHTON, M.D.,
AUGUSTA, GA.

MASSIVE edema of the vulva in pregnancy is quite rare, there being but ten references in the literature in the last twenty years. Usually multiple puncture, before labor is complete, allows enough collapse for delivery to take place through the vagina. However, there have been several cases reported in which the question of cesarean section is discussed.

An interesting fact is that the edema was of the labia majora while that pictured in two cases by Thorp and Wangeman was of the labia minora. In our case the inner surfaces of both labia majora became gangrenous and sloughed off, exposing the subcutaneous tissues in a craterlike ulcer which measured 2 by 10 cm. in the left labium, smaller in the right.



Fig. 1.—Photograph of vulva just prior to operation.

Case Report.—Primipara, colored, aged 23, stocky constitutional type, normal weight of 150 pounds at full-term pregnancy, admitted in labor at onset of first stage. About two weeks before, she began to have edema of feet, legs, and face. She had never attended clinic or had had any prenatal care. At about the same time she began to have headache, coinciding with sudden rapid enlargement of the abdomen. She began to have a few labor pains two days before entrance to the hospital and at the same time developed massive edema of vulva. She gave a history of fluid discharge from vagina for two days.

Physical examination of negro female in some distress, face slightly puffed, heart tones fair quality, lungs normal, abdomen very large. There appeared to be 2 fetuses with one fetal heart heard in the left upper quadrant, abdominal rate 134, another in the right lower quadrant, rate 125. One head was palpable in left

The patient was admitted to St. Mary's Hospital, Orange, N. J., for laparotomy; the preoperative diagnosis was (1) chronic appendicitis and (2) retroversion of the uterus. At operation a rather unusual picture was presented. The uterus was small and completely retroverted. The left tube appeared to be normal but the left ovary was enlarged to twice the normal size and contained numerous small cysts. A search of the right adnexal region revealed the complete absence of the right ovary and the presence of a stump of the right tube, $\frac{1}{2}$ inch long, buried in adhesions involving the broad ligament and the right parietal wall. These adhesions were rather firm in character and extended upwards to involve the cecum. The appendix was found to be only $\frac{3}{4}$ inch long, surrounded by adhesions at the ileocecal junction.

The diminutive appendix was removed, the cystic area of the left ovary resected, and the uterus suspended. The pathologic examination showed the appendix to contain polymorphonuclear leucocytes and lymphocytes scattered throughout the muscular wall. The piece of resected ovary was composed of small follicle cysts. The patient made an uneventful recovery and was discharged on the tenth post-operative day. Following the operation she was relieved of all abdominal symptoms. The menses occurred at twenty-six-day intervals, four days in duration, for the first two periods, and subsequently decreased to two and one-half days with corresponding diminution in flow.

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MEDICAL TOWER

VESICOVAGINAL FISTULA REPAIRED WITH RUSTLESS STEEL WIRE*

HENRY D. FURNISS, M.D., F.A.C.S., NEW YORK, N. Y.

CASE 1.—Woman, 24 years old, had been wearing a wishbone gold contraceptive pessary for four years. In spite of this she became pregnant in August, 1937. The pessary was removed; following this she developed a rectovaginal fistula. Evidently, one end of the pessary had become embedded in the rectovaginal septum.

She was first seen on Oct. 25, 1937, at which time a rectovaginal fistula, situated in the mid-line, at a point opposite the external cervical os of a normally positioned uterus, was found; this was $\frac{3}{4}$ cm. in the transverse, by $\frac{1}{2}$ cm. in the antero-posterior direction. On the right, there was a dense scar running from the cervix to the lateral wall of the vagina. The vagina was unusually tight. Operation was deferred because of pregnancy. She returned for operation in February, having had a midwife terminate the pregnancy in November.

Operation.—To obtain sufficient room, a left Schuchardt incision was made. With the index finger, of the doubly gloved left hand, in the rectum, the fistula was brought into view, and the scar tissue around the edges was dissected out. The rectum was then separated from the vagina. With four sutures of 00 Medrasil wire (nickel copper alloy) the rectal side of the fistula was closed, the sutures going to the mucosa, but not into the rectum. Four similar sutures were placed in the vaginal mucosa, at a right angle to the others. The Schuchardt incision was closed with catgut. Gas began to escape from the fistula on the third day, and there was fecal incontinence when the bowels moved on the fourth day. March 7, 1938, the vaginal sutures were

*Read at a meeting of the New York Obstetrical Society, March 8, 1938.

UNILATERAL ABSENCE OF THE FALLOPIAN TUBE AND OVARY

DANIEL R. MISHELL, M.D., NEWARK, N. J.

RECENTLY a case was observed at laparotomy in which the entire right ovary and major portion of the right tube were found to be absent. This rather unusual finding prompted a search of the literature and some very interesting facts and theories were revealed. This condition is sufficiently rare to be reported in detail.

A. M., aged 24 years, white, married one year, never pregnant, was first seen complaining of pain in the right lower abdominal quadrant. The pain was continuous, dull and aching in character, accompanied by intermittent sharp exacerbations, duration of symptoms eight months, becoming progressively worse. Eighteen months previous to the present illness the patient had an attack of severe pain in the right lower abdomen, duration one week, not accompanied by vomiting or rise in temperature, nor necessitating confinement to bed. Previous to this episode



Fig. 1.—Diagrammatic sketch with uterus pulled forward and to the right showing: (1) Absence of right adnexa, (2) adhesions extending to cecum and appendix, (3) cystic left ovary.

there was no history of any abdominal pain. The menstrual history was rather interesting. Menarche occurred at the age of thirteen; the periods were regular every twenty-eight days, duration four days, normal in amount, no dysmenorrhea. During the past year the patient noticed that the periods, although regular, were decreasing in the amount of flow. During the past four months the period consisted of slight staining, duration one day. It was also noticed that the abdominal distress became more intensified just prior to the onset of the menses. The past history revealed no previous operations or severe illnesses, no marked change in weight, no history of vaginal discharge or backache.

Upon physical examination the patient seemed well-developed and nourished and in good general health. Abdominal examination revealed an area of marked tenderness over the right lower quadrant, especially pronounced over McBurney's Point. Bimanual examination showed no evidence of inflammatory changes in the vulva or vagina; the cervix was quite small and pointed upwards, the corpus rather small and retroverted. The right adnexa were not palpable; the left ovary was moderately enlarged and prolapsed in the culdesac. Urine and blood examinations were normal. The Wassermann test was negative. A gastrointestinal series was essentially negative, the appendix not visualized.

TECHNIQUE

The full length of the male end of the punch is inserted into the cervical canal, with its female jaw on the outside. It is then maneuvered into position so that a specimen can be obtained from any desired portion of the cervix, whether it be the upper lip or the lateral sides.

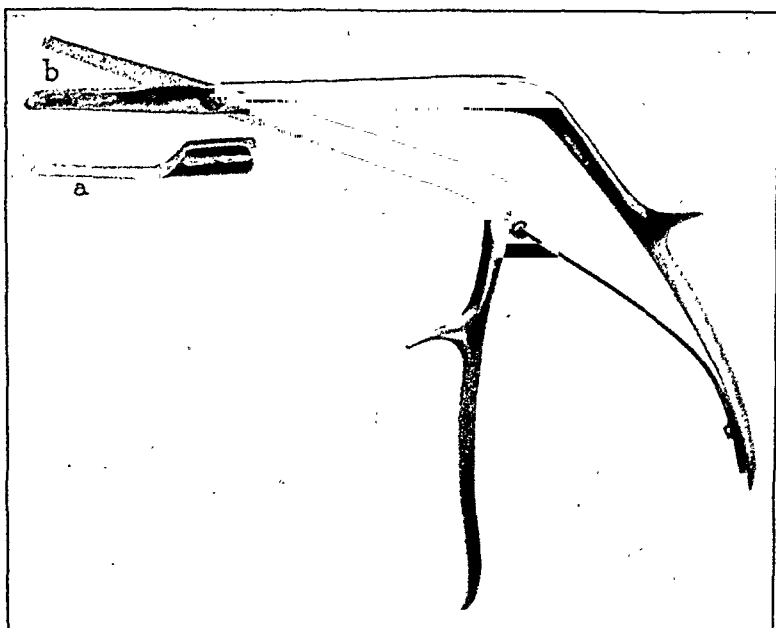


Fig. 1.—*a*, Removable basket spring; *b*, cutting jaws.

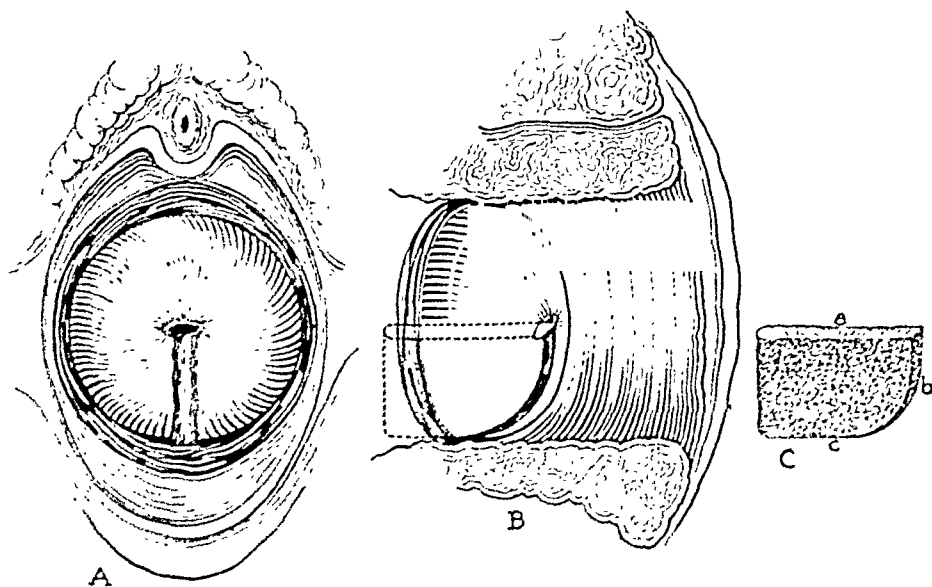


Fig. 2.—*A*, Front view, showing appearance of lower lip after biopsy. *B*, Lateral view, showing extent of biopsy from external os (*a*) toward an inward length of 16 mm. (*b*). *C*, Biopsy specimen measuring 16 mm. in length, 1 mm. in width, and 12.5 mm. in depth. *a*, Endocervix, *b*, cervical lip, *c*, portio vaginalis.

By means of a firm, forceful momentary pressure, and then by a sudden, more forceful pressure to the blades, the specimen is cut and forced into the spring basket. By sliding the basket off the lower jaw when the handles are extended, the specimen is simply removed. Should the specimen remain in the lower jaw, it can be pushed out with the thin end of the spring basket.

found free in the vagina; the ends had been shotted with one shot. The fistula was a bit smaller than when operated upon. The deeper metal sutures could not be felt either by rectum or vagina, but were shown by x-ray picture.

She will return in two or three months for operation. Then I shall make a bilateral Schuschart incision, put a Barnes' bag in the rectum, and by traction get a better exposure, and divide the rectal sphincter completely, posteriorly, to obviate either gas or fecal pressure. I dislike the necessity of doing a preliminary colostomy.

CASE 2.—Woman aged 31 years, had a complete perineal laceration, that was sutured immediately. Healing was good except for a small portion one-half inch from the introitus, one-sixteenth of an inch in diameter. Through this there was gas and slight fecal incontinence. The ends of the sphincter ani muscle were slightly retracted, and only when the bowels were loose was there any escape through the anal orifice proper.

Operation.—The scar tissue was dissected out and the anal mucosa separated from the vaginal structures. In this way the rectum was thoroughly mobilized. The opening was then $\frac{3}{16}$ of an inch in diameter. With interrupted sutures of Medrafil No. 60 sutures, so placed that they came just short of the rectal mucosa, this was closed. These were placed in tiers, thus building up the perineum, and approximating the ends of the sphincter ani muscles. The vaginal mucosa was closed with silkworm gut sutures. Healing was uneventful. On two occasions since leaving the hospital, there has been a slight serous discharge from the skin just above the anal orifice, lasting only a few days. She has experienced complete relief. For years I have endeavored to limit the use of catgut, because of the uncertainty of its absorption time, and the wound irritation caused by it. I have found the steel wire satisfactory likewise in closing a colostomy opening, and in the closure of the rectus fascia in several suprapubic cystotomies where drainage had been employed.

54 EAST 62ND STREET

A SCISSOR TYPE CERVICAL BIOPSY PUNCH*

HARRY O. MARYAN, M.S., M.D., CHICAGO, ILL.

ADEQUATE biopsies of the cervix uteri are essential for the accurate histopathologic diagnosis. The biopsy should be large enough to include the endocervix, the cervical lip, and the portio vaginalis portion.

It is not always easy to obtain adequate-sized biopsies with scalpel or scissors, even by a skilled technique. Therefore, I have devised a simple, scissorlike cervical biopsy punch to facilitate obtaining cervical biopsies.

This (Fig. 1) consists of a pair of handles with a spring and roller attachment, a shaft with a mortise or Bruening lock, and the male and female blades. Beneath the female jaw there is attached the removable basket spring which retains the specimen. The handles are so aligned that the object is always in direct line of vision. The spurs on the handles prevent the hand from slipping when pressure is applied. The solid, upper, male cutting blade, and the lower, open, female jaw measure 16 mm. in length, 4 mm. in width, and 5 mm. in depth, and may be opened to a distance of 12.5 mm., or 0.5 inch. The male blade is invaginated into the female jaw by means of a lower shaft, slotted to insure the proper aligning of the jaws.

This punch is capable of obtaining a biopsy 12.5 mm. or thicker from a dense cervix. The maximum specimen obtained (Fig. 2) will measure 16 mm. in length, 4 mm. in width, and 12.5 mm. in depth, and will include the three areas of the cervix: the endocervix, the cervical lip, and the portio vaginalis. A specimen of any desired length up to 16 mm. can be obtained.

*Presented at a joint meeting of the Chicago Gynecological and the St. Louis Gynecological Societies, February 19, 1938, Chicago, Ill.

Made by V. Mueller and Co., Chicago, Ill.

patients, such as those who suffer from yaws, leprosy, malaria, and relapsing fever, but a pseudopositive result due to pregnancy itself has not been definitely substantiated. An apparent problem is the detection of the syphilitic prenatal patient who gives a single negative Wassermann reaction and goes through pregnancy undiscovered, yet gives birth to a frankly infected infant. Different modifications of the Wassermann test have yielded variable results. There is need therefore for the universal adoption of a technique of proved value by laboratories and this must be brought about in all communities by cooperation between the groups immediately concerned. As another means of identification the more sensitive precipitation and flocculation tests can be used as confirmatory measures. Instances are known of cases in which the Wassermann test was consistently negative and the precipitation test positive, with the converse likewise true. A routine combination of these diagnostic agencies must be developed in order that the greatest number of latent syphilitic prenatal patients may be detected. Where discrepancies in both tests exist or where equivocal results are obtained, a thorough inventory is essential, which should include the repetition of the tests as well as a thorough scrutiny for significant data in the previous history of the patient. This may need to be extended to the husband and other children.

That pregnancy itself has an inhibitory and protective effect on syphilis has been contended by many authorities. It is unfortunate that up to the present time no test has been devised which is absolutely specific and completely sensitive, and there may be infrequent instances of completely negative results in prenatal patients who are undoubtedly syphilitic. Here, a carefully taken history and clinical manifestations irrespective of serologic findings may serve to detect some of these unusual cases. Again, where the disease is suspected serologic examinations repeated at short intervals may subsequently yield a positive result.

It is quite evident that inadequacies, no matter how rare, demand further standardization of processes and procedures and these should be, as already stated, the task of the agencies concerned. It has been shown very definitely that where the diagnosis of syphilis has been established not later than the fifth month of pregnancy efficient treatment will prevent the transmission of the disease from mother to offspring in approximately 95 per cent of the cases. Enough is known of such successful methods of treatment to assure the eradication of congenital syphilis in practically all instances and to make of the transmitted type of the disease a medical rarity. Again, it is the task of the medical man who undertakes the care of pregnant women to assume responsibility and to qualify himself accordingly, because the precautionary legislation already adopted by certain states will undoubtedly be invoked by others within a short time. The fight against syphilis should constitute one of the most important present-day aims of preventive medicine.

—M. D. Spicer.

Editorial

Syphilis and Pregnancy

THE world has become roused to the significance of syphilis in our social structure. A more or less insidious infection, its consequences well known, effective treatment a matter of common knowledge, yet we have hesitated to attack it in an open manner. The medical profession has been acquainted for a long time with the deplorable results of unrecognized and untreated manifestations of this world-wide affliction. Progress in its handling received a great impetus in recent times by the outstanding discoveries of Wassermann and Ehrlich, and their co-workers and successors. Yet evidently, publicity was necessary in order to disseminate this valuable technical knowledge and apparently this is now being accomplished. Governmental agencies have come to the assistance of the medical profession both here and abroad. An aroused public interest has stimulated legislative enactments such as the laws recently placed on the statute books by New York and other states, calling for premarital examinations and serologic tests in pregnancy.

The responsibility for carrying out these measures and their interpretation rests upon the doctor and he must prepare himself accordingly. How well is he equipped to do this? In other words, to eradicate congenital syphilis with its attendant loss of life and the physical disabilities which develop in those infants who survive. The diagnosis of the disease in prospective parents and its adequate treatment are of equal importance.

Since the highest attack rate occurs between the sixteenth and thirty years of life, which corresponds in a measure with the active childbearing period, the incidence of syphilis in the pregnant woman is a problem which merits attention. Most well conducted hospital clinics have for many years carried out serologic tests in their patients but the clientele of the private physician has not been subjected to similar methods of diagnosis. The legal measures now being introduced will enforce upon all pregnant women the serologic tests. In a minority, certain clinical manifestations of the disease may be manifest but a physician must familiarize himself with these so that, if present, they may be recognized. Serologic tests, as a matter of fact, are of no aid in the early stage of the primary lesion and in many instances of the later stages. The innocuous erosive chancre of the cervix requires dark-field studies for confirmation. It has been found that the great majority of syphilitic prenatal patients are clinically latent and that a significant history can be obtained in less than half. This shows the need for routine serologic tests. Positive reactions may occur in nonsyphilitic

CHICAGO GYNECOLOGICAL SOCIETY

JOINT MEETING WITH THE ST. LOUIS GYNECOLOGICAL SOCIETY

MEETING OF FEBRUARY 19, 1938

The following papers were presented:

A Scissor Type Cervical Biopsy Punch. Dr. Harry O. Maryan. (For original article, see page 707.)

Cesarean Section—An Analysis and a Discussion. Dr. Wm. C. Stude.

Results of Cultures of the Uterus at Cesarean Section. Dr. T. K. Brown.

Etiology of Cervicitis. Dr. Melvin A. Roblee. (For original article, see page 1039, June, 1938, issue.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MARCH 18, 1938

The following papers and discussions were presented:

Rhythmic Changes in the Skin Capillaries and Their Relation to Menstruation. Dr. John I. Brewer. (For original article, see page 597.)

Unpredictability of the Phenomena Accompanying the Menstrual Cycle in Normal Women. Drs. Julius E. Lackner, Hans Wachtel, and Samuel Soskin. (For original article, see page 612.)

Large Degenerated Subserous Myoma. Dr. Irving F. Stein.

WASHINGTON GYNECOLOGICAL SOCIETY

MEETING OF NOVEMBER 27, 1937

The following papers and discussions were presented:

The Use of Vitamin E in the Management of Repeated and Threatened Abortions. Dr. J. Keith Cromer.

The Relative Value of Pure Oxygen and of Carbon Dioxide Mixtures in Experimental Resuscitation. Drs. N. J. Eastman, R. B. Dunn and Joseph Kreiselman. (For original article, see page 571.)

NEW ORLEANS GYNECOLOGICAL AND
OBSTETRICAL SOCIETY*MEETING OF JANUARY 21, 1938*

The following papers were presented:

The Elliott Treatment of Pelvic Inflammatory Diseases of Women as Used in the Office of Private Practice. Dr. Earl C. Smith.

Ruptured Hemorrhagic Ovarian Follicle Complicating Acute Appendicitis. Dr. L. A. LeDoux.

MEETING OF APRIL 21, 1938

The following paper was presented:

Granulosa Cell Tumor of the Ovary. Dr. Eugene H. Countiss. (For original article, see page 680.)

Society Transactions

NEW YORK OBSTETRICAL SOCIETY

MEETING OF JANUARY 11, 1938

Endometrial Hyperplasia (Puberty) Adenocarcinoma, Fifteen Years' Follow-Up. Case Report. Dr. Vincent P. Mazzola. (For original article, see page 698.)

Congenital Absence and Traumatic Obliteration of the Vagina and Its Treatment with Inlaying Thiersch Grafts. Dr. Virgil S. Counsellor, Rochester, Minn. (By invitation.) (For original article, see page 632.)

The Persistence of Gonococcal Infection in the Adnexa. Drs. W. E. Studdiford, W. A. Casper, and E. M. Scadron.

The Dilating Bag in Obstetrics. Dr. Edward G. Waters. (For original article, see page 639.)

MEETING OF FEBRUARY 8, 1938

The following papers were presented:

The Diet of the Pregnant Woman. Dr. E. V. McCollum, of Baltimore, Md. (read by invitation). (For original article, see page 586.)

Fetal Respiration and Its Bearing Upon Injuries of the Newborn. Dr. Franklin F. Snyder, of Baltimore, Md. (by invitation).

MEETING OF MARCH 8, 1938

The following papers were presented:

Vesicovaginal Fistula Repaired With Rustless Steel Wire. Case report by Dr. H. D. Furniss. (For original article, see page 706.)

Some Present Day Problems in Syphilis and Pregnancy. Dr. J. R. McCord, of Atlanta, Ga., by invitation.

Vesicovaginal Fistula After Complete Abdominal Hysterectomy. Dr. Albert H. Aldridge.

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF FEBRUARY 3, 1938

The following paper was presented:

Carcinoma of the Cervix. Dr. Norman F. Miller and Dr. Clair E. Folsome. (For original article, see page 545.)

nosis he considers the functional capacity of the heart as one of the best indices, and has grouped his cases according to the classification of the American Heart Association.

There is a thorough discussion of congestive heart failure, and he feels that a death rate from 2 to 3 per cent among gravidocardiacs appears irreducible at the present time. Congestive heart failure he states is a factor in 70 per cent of the cases fatal from this complication. The material he has worked over indicates that the prognosis in heart disease during pregnancy grows worse with advancing age, although it does not exceed what might have been expected among women without heart disease, and he states that there is no evidence that pregnancy as such has increased this death rate.

The effects of various cardiac lesions on prognosis are fully described. The author discusses the various factors offered to show that childbearing influences the rheumatic heart or pathologic processes in the heart, and presents his own ideas as to the onset and development of congestive failure. The various complications of valvular heart disease during pregnancy from his own experience and from the literature are discussed, with an analysis of the different views held.

There is a splendid chapter on the management of pregnancy and rheumatic heart disease, and the author ascribes credit to improved prenatal care for the reduction in the death rate. He considers as an indication for the interruption of pregnancy heart failure which does not respond to treatment. Various methods of delivery of cardiac patients are presented with statistical reviews from the literature, and the summary is quite in accord with the conservative attitude of most American clinics, especially as regards cesarean section and sterilization. In discussing the various types of anesthetics and analgesic agents, he properly states that the choice depends upon individual preference and individual study of the patients. The following chapters of this volume discuss the nonrheumatic heart diseases such as bacterial endocarditis, cardiovascular syphilis, congenital heart disease, degenerative heart disease, kyphoscoliotic disease and thyroid heart disease. Of particular interest in the chapter on degenerative heart disease is the manner in which the author has developed the recent views regarding the interrelationship of the increase of blood pressure in toxemia, essential hypertension and cardiovascular disease, a subject in which he and his associates have independently come to quite similar conclusions with those which Herrick has propounded.

This volume is so all inclusive of the various phases of the subject, so fully documented and moot points in the literature are so thoroughly analyzed, that it should be useful as a working manual as well as a source of reference to all cardiologists and obstetricians.

—Philip F. Williams.

The contributions from this well-known French clinic of the year 1937 appear under the title of *Leçons du Jeudi Soir à la Clinique Tarnier*.² Fifteen contributions are published in this volume, and they may be considered, in so far as clinical practice is concerned, as expressing the present views of this French School. Brindeau, the chief of the clinic, opens the volume with a history of cesarean section. He concludes that the cervical segment operation permits a trial of labor and will supersede hysterectomies or the operation of Portes in many instances. Metzger discusses the third stage of labor, and counsels conservatism. Lanteuoul discusses pregnancy complicated with myoma, and concludes that indications for operation are extremely limited, and during pregnancy or labor he insists only on myomectomies. He states that, on the contrary, during the puerperium, it is the attitude of the clinic to have recourse to hysterectomy.

Suzor describes the treatment of toxemia and Hauch recounts their experiences in various trials of analgesia and obstetric narcosis. The use of obstetric analgesia has been increased in their clinic in five years to from 50 to 70 per cent of the women. There has been almost an equal increase in the use of inhalation anesthesia with the use of barbiturates or agents of like nature. Hauch concludes that they have

²*Leçons du Jeudi Soir à la Clinique Tarnier*. Published under the direction of A. Brindeau. One volume, 318 pages, 69 figures. Vigot Frères, Paris, 1938.

Department of Book Reviews

CONDUCTED BY ROBERT T. FRANK, M.D., NEW YORK

Review of New Books

Obstetrics

This volume on *The Heart in Pregnancy*¹ by Jensen is an outstanding discussion both from the standpoint of cardiology and obstetrics. The range of topics is quite comprehensive, and an analysis of each factor is so detailed that the book is unusually complete, and must be regarded as a volume of especial value. The work represents an intensive study of the heart cases complicated by pregnancy seen in the St. Louis Maternity Hospital over a period of eight years, and in addition covers such a wide range of the literature that the bibliography comprises twenty-six pages of references.

Dr. Jensen divides his book into three parts: the effect of pregnancy on the normal heart; abnormal cardiac impulse formation during childbearing; and organic heart disease and pregnancy. The subdivision of these various headings brings up a study on the increase of cardiac work during pregnancy. Here Jensen regards two facts as standing out among all the evidence, namely: that in pregnancy the increase in metabolism may well be the cause of cardiac overwork and that the volume of the circulating blood is increased often out of proportion to the increase in weight. All factors which have largely been assumed to increase the work of the heart during pregnancy have been fully considered. In regard to the mechanism whereby the heart meets these increased demands, he discusses increased peripheral resistance, the pulse, the cardiac output in pregnancy, oxygen utilization, and circulation time. The author feels that there is a regrettable inconsistency in opinions expressed about most of these subjects and regards them as a fertile field for future researches.

The physiology of the normal heart during normal pregnancy opens with a discussion of the long dispute over the tendency of the heart to increase in size in pregnancy, continues with the roentgen examination of the heart and the electrocardiogram as a means of examination. He notes that the electrocardiogram undergoes changes suggestive of various axis deviations but the irregularity with which the heart is displaced precludes any regular occurrence or sequence of the variations reported.

In a short second part of the book the author discusses the abnormal cardiac impulse formation during pregnancy, taking up tachycardia, bradycardia, extrasystoles and auricular flutter and heart block. As his personal experience he believes there is a slowing of the puerperal pulse as compared to that in pregnancy, a return to normal from the increased pulse rate incidental to pregnancy, with a prevailing basal rest level of the pulse rate.

In the third part of the book Jensen discusses rheumatic heart disease and pregnancy. Commenting on the statistics of rheumatic disease, and the incidence of rheumatic heart disease and pregnancy, he notes that the recorded death rate gradually has been reduced from 8 to 10 per cent to near 2 per cent, and the average death rate in a large series of cases is 4.3 per cent. He notes that heart disease ranks among the four or five most important causes of maternal death. For prog-

¹The Heart in Pregnancy. By Julius Jensen, Assistant Professor of Clinical Medicine, Washington University School of Medicine, etc. 371 pages. The C. V. Mosby Company, St. Louis, 1938.

eighth edition has been most thoroughly revised, a task requiring a good deal of rearranging and the rewriting of several sections. Holland may well be proud of the fact that in spite of inclusion of all the more recent developments in obstetric science and of the addition of many new illustrations and three color plates, the book has grown by only fifteen pages. Thus it remains a manual in the true meaning of the word, ready at hand for any desired information which it supplies in the exact and succinct language of the text, by means of excellent illustrations and as well in form of brief abstracts of correlated literature, appended as Guide to Further Reading at the end of each of the nine sections.

That this volume actually has been brought up to date is rather convincingly demonstrated by the authentic evaluation of prontosil in obstetric practice and the favorable consideration of the classification of pelvises as elaborated by Caldwell and Moley.

—Hugo Ehrenfest.

In a series of monographs, explicitly designed for the benefit (Fortbildung) of practitioners, as volume 24, is presented this complete summary of available information concerning the *Rôle of Vitamines (especially A and C) in Pregnancy*.⁶ Its author, Gerhard Gaehtgens, is particularly competent to prepare such a summary because our present knowledge in this respect to a great extent must be credited to his own investigations. In a brief résumé of the contents of this work he emphasizes the fact that clinical and experimental experience proves that there exists an indivisible biologic complex between pregnancy and the puerperium. In the maternal systemic changes in both phases, the purposeful adaptation to the needs of the child is evident. This is brought about by vegetative and hormonal regulation as well as by various vitamins. Among them Gaehtgens discusses in detail vitamins A and C, fully aware that further research is required in regard to others of the vitamins.

In this monograph the obstetrician will find much new information, in part of great practical importance.

—Hugo Ehrenfest.

Arnoldo de Moraes' Manual, *Propedeutica obstetrica*,⁷ of Obstetrics has reached its fifth edition since 1924. It is particularly aimed to fill the wants of practitioners and students and therefore emphasizes those interventions which do not fall into specialistic hands. As elsewhere, throughout South America, increasing interest is shown in prenatal care. The format, illustrations and text conform to previous editions. The book is well planned, sufficiently detailed, and is evidently a favorite.

—R. T. Frank.

Pre- and Postnatal Care

These *Collected Studies on the Dionne Quintuplets*⁸ represent the cooperative work of nine staff members of the St. George's School for Children Study of the University of Toronto. The six separate studies, combined in this volume, deal respectively with biology, mental growth, early social development, development of self-discipline, routine training, and early development in spoken language of these remarkable quintuplets.

Of particular interest to the obstetrician is the exhaustive biologic study made by John W. MacArthur and Norma Ford, which leads them to the definite con-

⁶*Der Vitaminhaushalt in der Schwangerschaft mit besonderer Berücksichtigung der Vitamine A und C.* By Dr. Med. Gerhard Gaehtgens, Universitätsfrauenklinik zu Leipzig. With 21 illustrations, 161 pages. Published by Theodor Steinkopff, Dresden, 1937.

⁷*Propedeutica obstetrica.* Prof. Arnoldo de Moraes, Professor Cathedrae de Clinica Gynecologica da Faculdade Nacional de Medicina da Universidade do Brasil. Edition 5, with 499 pages, 155 illustrations. Grafica Suer, Rio de Janeiro, 1937.

⁸*Collected Studies on the Dionne Quintuplets.* By W. E. Blatz, N. Chant, M. W. Charles, M. I. Fletcher, N. H. C. Ford, A. L. Harris, J. W. MacArthur, M. Mason, and D. A. Millchamp. Illustrated. The University of Toronto Press, Toronto, 1937.

as yet not discovered a satisfactory analgesic agent. The social aspect of obstetrics is discussed by Vandescall who analyzes the maternity benefits given in France and other countries of the world. Among the other topics discussed may be mentioned rupture of the uterus, comparative merits of forceps and version, obstetric shock, syphilitic lesions in the newborn child.

As usual this volume of finely prepared material reflects the excellency of the work performed in this obstetric center.

—Philip F. Williams.

Only two years have elapsed since publication of the preceding edition of this *Synopsis of Obstetrics and Gynaecology*³ by Bourne but progress in these two fields of late has been rapid. This latest edition has been thoroughly revised and brought up to date as evidenced, e.g., by inclusion of discussions of mandelic acid and prontosil.

The systematic and remarkably comprehensive presentation of an immense amount of material in precise and consistently clear language, aided by excellent diagrammatic sketches at the bottom of the page, has been duly emphasized in reviews of preceding editions. Both advice and warning always are offered in the form of terse statements.

The American reader will discover but few points not entirely in agreement with our common practice, as for instance, giving an enema immediately before forceps extraction, the instrument being applied with patient lying on her side. The author exhibits noteworthy conservative views in regard to the value of organotherapy in gynecologic practice.

This little volume can unreservedly be recommended to student and practitioner.

—Hugo Ehrenfest.

This most exhaustive discussion of the *Diseases of Pregnant Women*⁴ by Henri Vignes is presented in form of monographs. We had occasion to describe in this JOURNAL the two preceding volumes of this series, dealing respectively with (1) Disorders of the Digestive Tract, and (2) Diseases of Liver and Pancreas, and Disorders of Nutrition, etc.

This third monograph is devoted to the *Affections of the Skin*. We can only repeat what we have stated before, namely, that the familiarity of the author with existing literature is amazing. Every known effect of pregnancy on either the physiology or pathology of the skin, obviously including hair and nails, is thoroughly discussed from the viewpoint not only of etiology and symptomatology but also of therapy.

As pointed out in previous reviews, the underlying arrangement of this truly encyclopedic presentation (according to the different organs of the body) obliges consideration of subjects such as lepra, erysipelas, and puerperal scarlatina. However, a carefully prepared index easily overcomes this inevitable shortcoming of the underlying scheme.

This valuable addition to obstetric literature can be qualified as incomparable, simply because no similar book of ready reference has ever been published in any language.

—Hugo Ehrenfest.

Eden-Holland's *Manual of Obstetrics*,⁵ first published in 1906, requires neither description nor recommendation. It seems, however, worth noting that this new

³*Synopsis of Obstetrics and Gynaecology*. By Aleck W. Bourne, Consulting Obstetric Surgeon, Queen Charlotte's Hospital, etc. Edition 7, fully revised with numerous diagrams, 452 pages. William Wood and Company, Baltimore, 1937.

⁴*Maladies des femmes enceintes*. Vol. III. *Affections de la peau*. By Henri Vignes, with collaboration of F. Hanoun and G. Vial. 202 pages. Masson & Cie, Éditeurs, Paris, 1937.

⁵*A Manual of Obstetrics*. By Thomas Watts Eden, Consulting Obstetric Physician to Charing Cross Hospital, etc., and Eardley Holland, Obstetrical and Gynaecological Surgeon, and Lecturer on Obstetrics and Gynaecology, the London Hospital, etc. Edition 8, with 12 plates and 398 illustrations, 765 pages. J. & A. Churchill, Ltd., London, 1937.

Toxemias of pregnancy are divided into six groups. It is evident that the Liverpool Clinic practices very conservative therapy in these conditions. Suggestions are made as to diagnosis of the diseases of the products of conception and some extremely well executed roentgenographs of abnormal fetuses are found here.

In discussing venereal diseases in pregnancy, the author remarks that the treatment of syphilis in pregnancy is designed to prevent infection of the fetus and not necessarily to cure the mother. He recommends alternating series of injections of arsenic and bismuth.

There is ample discussion of the conditions which demand the induction of labor and the methods of these procedures.

The use of the x-ray in antenatal management forms the subject matter of a small, concise chapter, although the subject of pelvic and fetal mensuration is studied rather briefly. The author does not hesitate to express his opinions on contraception and sterilization and gives full consideration of the indications and methods of both.

The subject of care during convalescence after childbirth is extremely well handled. He regards the management as being divisible into prophylactic and active methods. The prophylactic methods include those previously discussed in the antenatal periods and a succinct summary of intrapartum care. In this section there is a series of illustrations picturing exercises of various types to restore body tone.

This is an excellent though brief discussion of prenatal study and postnatal management.

—Philip F. Williams.

*The Baby's First Two Years*¹¹ is a book intended as a guide to young mothers. It discusses the surroundings of the child, its growth and development, with instructions for hygiene and nutrition, and a short discussion of the more common complaints to which the child in infancy may be subject.

There is an excellent chapter on a typical day from a child's life which should do much toward training the young mother to a definite routine. The book closes with various records and recipes which should be of help. The photographic illustrations add much to the value of the book. One can well recommend this book to recent obstetric patients.

—Philip F. Williams.

Gynecology

Dr. Titus has written a very fine monograph, *Diseases of Women*,¹² to meet the gynecologic problems of the general practitioner. The subject matter, presented simply and concisely, stresses the need of early and accurate diagnosis. He has gone into particular detail regarding the office treatment of such gynecologic conditions as may be handled in ambulatory patients. The text follows a standard classification of arrangement discussing by organs, the infections, tumors, and displacements to which they are subject. The nonoperative handling of retrodisplacements of the uterus and use of pessaries is fully considered. In discussing ectopic pregnancy he suggests colpopuncture by needle and syringe, a method which should only be used if preparation for abdominal operation is present. He emphasizes the need for transfusion in these cases. The author wisely cautions against the indiscriminate administration of the various glandular substances in his excellent consideration of hormonal disturbances. He offers the general practitioner a working schedule of the essential steps necessary in studying sterility, and points out the

¹¹*The Baby's First Two Years*. By Richard M. Smith, Assistant Professor of Pediatrics and Child Hygiene, Harvard Medical School and School of Public Health, etc. With illustrations, 121 pages. New and revised edition. Houghton Mifflin Company, Boston, 1937.

¹²*Diseases of Women, for the General Practitioner*. By Paul Titus, M.D., Obstetrician and Gynecologist to the St. Margaret Memorial Hospital, Pittsburgh, etc. Edited by Morris Fishbein, M.D. Illustrated, 320 pages. National Medical Book Co., Inc., New York, 1937.

clusion that the Dionne quintuplets are a set composed entirely of identicals, derived from a single ovum. They are of the same sex, have all the same blood group (O), and are nearly indistinguishable in eye color, hair color, texture, and form, and in degree of skin pigmentation. There is a striking likeness of the finger, palm, and sole prints. Any pair of them are as alike as identical twins. A detail in the history suggests the early abortion of a sixth embryo, whose survival might have bridged a noticeable gap between Annette and Emilie.

Some 60 other cases of quintuplet births were traced in medical literature. The Dionne quintuplets, however, are unique as having survived as an unbroken set, an achievement made possible by the practice of modern pediatrics and the untiring efforts of their attending physician, Dr. Allan Roy Dafoe, and his aides. It is planned to extend these studies in other essential ways as the children grow older.

—Hugo Ehrenfest.

After a lapse of six years the authors present the fifth edition on, *The Management of the Sick Infant and Child*,⁹ thoroughly revised to include the many advances in this specialty. The subject matter is divided into three parts. The first deals with such general considerations of the subject as vomiting, diarrhea, nutrition, hemorrhage, convulsions, fever and prematurity; the second part discusses regional and infectious diseases, behavior problems, allergy and disorders of internal secretion; while the third part describes methods and techniques of treatment, formulas and prescriptions for diets for normal and abnormal conditions. The section on drugs includes a consideration of dosages and a collection of prescriptions which arose in the author's private practice or the children's wards of various hospitals.

Of particular interest to obstetricians should be the consideration of the subject of intracranial hemorrhage, the ideas presented on the topic of prematurity, skin diseases of the newborn, vulvo-vaginitis, dysfunctions of the various glands of internal secretion and syphilis. There are many points discussed under methods of treatment which are germane to the practice of obstetrics, if the obstetrician retains the care of the newborn. It is interesting to note that the authors are cautious in their recommendations for the use of sulfanilamide for disorders of the sick infant.

—Philip F. Williams.

The importance of prenatal care and the significance of care after birth are emphasized in this small book, *Prenatal and Postnatal Management*,¹⁰ which is an excellent manual on preventive medicine in obstetrics. Dr. Wilson gives an excellent system for history, examination, and management of normal pregnancy, and then proceeds to what might well be termed prenatal study of abnormal pregnancy. Under placenta previa he mentions amniography and cystography as aids in diagnosis of placenta previa. Both methods are considered of questionable value in this country. He gives a concise consideration of local maternal conditions which are likely to affect parturition in discussing malformations of the soft parts as well as those of the bony pelvis.

The various systems are reviewed in a chapter on the general maternal conditions affecting pregnancy. The author does not feel that induction of premature labor is in place in heart disease. He emphasizes the need for a complete hemogram in pregnancy. For the various infections of the urinary tract the author recommends mandelic acid and ammonium citrate in pregnancy, reserving in-dwelling catheters for extremely persistent cases. In discussing the endocrine system he states that ovarian deficiency may be the cause of primary uterine inertia in labor, and suggests studies and treatment during pregnancy to avoid consequent inertia.

⁹*Management of the Sick Infant and Child*. By Langley Porter, Dean, University of California Medical School, and Professor of Medicine, etc., and William E. Carter, Director, University of California Hospital, Out-patient Department, etc. Edition 5, revised, illustrated, 874 pages. The C. V. Mosby Company, St. Louis, 1935.

¹⁰*Prenatal and Postnatal Management*. By J. St. George Wilson, Hon. Obstetric and Gynaecological Surgeon, Royal Infirmary, Liverpool, etc. With a foreword by Sir Comyns Berkeley. With 80 figures and a color plate, 206 pages. William Wood & Co., Baltimore, 1937.

patient, and conclude that the outlook for the woman with gonorrhea has been very much brightened by the development of the combined heating procedures described.

—Philip F. Williams.

Bonnet has presented for his French colleagues a very clear description of the Rubin test under the title of *Insufflation tubaire kymographique*,¹⁵ to which both Professor Faure and Dr. Rubin have added forewords. He has made certain minor modifications of the Rubin apparatus and has constantly employed the kymograph to obtain graphic records of his results. The graphs are quite similar to those first published by Rubin and his explanations are based on conclusions which Rubin has popularized. He discusses the physiology of the tubes and ovaries in relation to the test, especially, in regard to x-ray stimulation of the ovarian function and its relation to the peristaltic movements of the tube.

From the standpoint of therapy he has found that 20 per cent of his patients with tubal spasm became pregnant after treatment, and 21 per cent of his patients with altered patency became pregnant after repeated treatments. He discusses this method in contrast to such other forms of treatment as salpingostomy and the use of lipiodol.

—Philip F. Williams.

Miscellaneous

In his book on *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases*,¹⁶ Dr. Young has given a fundamental study of the greatest importance. There are introductory chapters on the history of hermaphroditism and its embryology. On the latter he had the advice of Streeter and Hartman, and standard sources have been freely used.

The main chapters are on personal cases described in detail. There are six cases of male pseudohermaphroditism, five of which had vaginas opening into the urethra. Four female pseudohermaphrodites showed enlargement of the adrenal cortex, large clitoris, and persistent urogenital sinus. There are three cases in which in young girls the adrenals were resected. Of these only one showed an increase in estrogenic substance in the urine. A number of unusual "practicing" hermaphrodites are described and one true hermaphrodite is recorded together with the literature of twenty cases.

An adrenal tumor in a patient suffering from the adrenogenital syndrome was successfully removed. Ovarian growths with masculinization, prostate in female pseudohermaphroditism, hyper- and hypogenitalism, as well as gynecomastia are dealt with. The subject of hypospadias, epispadias, cryptorchidism and atresia ani are fully discussed. The final chapter might be called an endocrine summary.

This book is not only valuable because of the large amount of case material but likewise for the minute and beautifully illustrated operative technique (drawn by Didusch) used in the treatment of these numerous cases. A full description of the simultaneous posterior exposure of both adrenals devised by Young is included. Everyone interested in any of the subjects dealt with should consult this important volume.

—R. T. Frank.

*The Adrenal Cortex and Intersexuality*¹⁷ is a symposium in which a number of different specialists have combined. The foreword is by Sir Walter Langdon-Brown

¹⁵*Insufflation tubaire kymographique par la méthode de Rubin.* By Louis Bonnet, ancien chef de clinique gynécologique à la Faculté de Médecine de Paris. Illustrated; 96 pages. G. Doin & Cie, Paris, 1937.

¹⁶*Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases.* By Hugh Hampton Young, Professor of Urology, Johns Hopkins University, etc. With 379 plates containing 534 drawings by William P. Didusch; 649 pages. Williams and Wilkins Company, Baltimore, 1937.

¹⁷*The Adrenal Cortex and Intersexuality.* By L. R. Broster, Clifford Allen, H. W. C. Vines, Jocelyn Patterson, Alan W. Greenwood, G. E. Matrian, and G. C. Butler. With a foreword by Sir Walter Langdon-Brown. Illustrated, 215 pages. Chapman & Hall, Ltd., London, 1938.

necessity for such conditions to be handled by a group rather than by one man. Of particular benefit to the gynecologic patient whose preparatory and postoperative care must be handled by the general practitioner, are the two final chapters on these subjects; they contain instruction which is frequently lacking in the care of such patients.

The book is highly recommended to the general practitioner whose practice includes the care of women with gynecologic ailments.

—Philip F. Williams.

The fifth edition of this well-known classic, *Operative Gynecology*,¹³ has been entirely revised and reset. It appears six years after the previous edition. In addition to the two Crossens, a chapter on the Intestinal Tract in Relation to Gynecologic Surgery and a chapter on Anesthesia in Gynecologic Surgery were written by Dr. H. S. Brookes, Jr. Two hundred new illustrations have been added, now numbering twelve hundred and sixty-four.

In the main, the same methods of approach which have made this book so valuable, have been maintained, the questions posed being whether operation is needed, if so what operation should be selected, and finally, the treatment before and after operation. This volume is by far the most complete and comprehensive one in existence on operative technic in gynecologic surgery. It has proved so valuable because no details have been neglected and therefore either the occasional operator or the gynecologist can, without trouble, find all necessary directions concerning the choice and execution of an operation within its pages. Included also is collateral information such as the details of radium and radiation treatment.

The contents are so huge that no attempt at detailed review can be undertaken. Suffice it to say that I have been able to find a large number of operations selected at random. The authors do not hesitate to indicate their preferences but on the other hand do not slur such operative techniques as they themselves probably do not utilize. In a book strictly confined to surgical techniques the chapter on nervous and mental symptoms in relation to gynecologic surgery is particularly apt and valuable. This book, as heretofore, can be most heartily recommended to the profession.

—R. T. Frank.

The abstracts and discussions of papers presented at the First International Conference on Fever Therapy in New York City in 1937 are presented in this volume, *Fever Therapy*,¹⁴ which has been edited by the members of the American Committee.

The subject matter offers in English, French, and German discussions on the subject of fever therapy from many standpoints. The opening section deals with the physiology and pathology of this mode of treatment. The complications and reactions to the therapy, and preparation of patients for such therapy are presented. Fever therapy of such miscellaneous diseases as cardiovascular disease, acute rheumatic fever and dengue are subsequently discussed. The employment of the method in ocular disturbances, neurology and psychology and other systemic disease is then taken up. A symposium of eight papers deals with the subject of the treatment of syphilis by fever therapy.

Of particular interest to the gynecologist is the symposium of twelve papers discussing fever therapy of gonococcal infections. Bierman and Horowitz contribute an article on the treatment of gonorrhea of women by means of the combined systemic and additional local heat. They state that the average number of treatments necessary to eradicate the gonococci from their last series of cases was 1.4 per

¹³*Operative Gynecology*. By Harry Sturgeon Crossen, Professor Emeritus of Clinical Gynecology and Obstetrics, and Robert James Crossen, Assistant Professor of Clinical Gynecology and Obstetrics, Washington University School of Medicine, etc. Edition 5, entirely revised and reset. With 1264 illustrations including three color plates, and 1076 pages. The C. V. Mosby Company, St. Louis, 1938.

¹⁴*Fever Therapy*. Abstracts and discussions of papers presented at the First International Conference on Fever Therapy, March 29-31, 1937. College of Physicians and Surgeons, Columbia University, New York, 486 pages. Paul B. Hoeber, Inc., New York, 1938.

our enormously greater problem are also discussed. This book should be widely read by physicians and public health workers, nurses, and social hygienists, for there is little that is controversial and much which is authoritative and stimulating in the material presented.

—Philip F. Williams.

This book, *Death Rides With Venus*,¹⁹ is prepared by the Director of the Social Hygiene Foundation of Cleveland, and presents a discussion of venereal diseases in a floridly popular style. Undoubtedly the author's position has made him thoroughly familiar with the bald aspects of the social disease problems as they exist today. With the utmost frankness he discusses the various phases of the problem as they have come to him. The ravages of gonorrhea he discusses in a chapter entitled, "Malignant Coffee Beans"; while the horrors of prostitution are brought out in a chapter entitled, "All Whores Are Lousy." The relationship of the American citizen to this problem of social disease is taken up in the final chapter. A reading of this final chapter should dissipate any smugness or disinterest in a problem which affects labor, business, and the tax bill.

—Philip F. Williams.

The Reverend Tyrer's long years as a marriage counsellor have resulted in the publication of his teachings in this book, *Sex Satisfaction and Happy Marriage*.²⁰ Here Reverend Tyrer discusses the many questions and problems that have come to him, which relate in the most part to sex education for engaged couples, as well as such problems of married people as abortion, birth control, impotence, and frigidity. All of these topics are presented in a thoroughly understandable manner which should suggest a simple line of explanation by the physician or clergyman when confronted with like problems. In the final chapter the Reverend Tyrer moves from the discussion of love, sex, and marriage to a number of small items most of which come up almost daily in conversations with obstetric and gynecologic patients.

Dr. Robert L. Dickinson in a foreword commends the book as an excellent illustration of the standard medical work adapted to the use of the laity.

—Philip F. Williams.

In *The Single Woman and Her Emotional Problems*,²¹ a splendid presentation of the psychosexual problem of women, Dr. Hutton offers help to both the woman herself and her medical advisor. In this edition of the book she has added a chapter explaining the psychologic terms used in the text, which should be of help to lay readers in comprehending the later discussion. That this book was needed is evidenced by the fact that it has appeared in a second English, a Dutch and a Norwegian edition. The single women, of whom there are many in our present mode of life, have problems peculiar to themselves, developing as a result of both normal and abnormal relationships. This book deals in a sympathetic and sane manner with these emotional friendships and sexual problems. The reading of the book should instill sympathy and understanding in a medical advisor, and provide definite and constructive help for the lay reader of the class for whom it is intended.

This edition receives the same warm commendation that was given to its predecessor.

—Philip F. Williams.

¹⁹*Death Rides with Venus*. By Arthur C. Palm. The Greystone Press, New York, 1937.

²⁰*Sex Satisfaction and Happy Marriage*. By the Reverend Alfred Henry Tyrer, Clergyman of the Protestant Episcopal (Anglican) Church. Foreword by Robert L. Dickinson, M.D., New York. Emerson Books, Inc., New York, 1938.

²¹*The Single Woman and Her Emotional Problems*. By Laura Hutton, Physician, Tavistock Clinic, London. Edition 2; 173 pages. William Wood and Co., Baltimore, 1937.

of the University of Cambridge. The clinical study of the adrenogenital syndrome has been dealt with clinically and surgically by Broster; the psychologic by Clifford Allen. A scientific study of this syndrome includes the histologic observation by Vines and biochemical ones by Jocelyn Patterson as well as Marrian of Toronto.

The book contains a wonderful amount of clinical material. The surgical results following adrenalectomy are remarkably good (33 adrenalectomies with but one death), and yet the book as a whole is extremely disappointing. This is due to the fact that particularly in the clinical chapter the work-up is frequently defective and the conception of what actually constitutes a clear-cut adrenogenital syndrome is beclouded by the fact that a number of doubtful and merely allied conditions are included. The follow-up likewise is frequently insufficient and criteria loosely drawn. The surgical approach has been changed. In his earlier publication Broster used the transthoracic route. He has now changed to the lumbo-abdominal approach, in most cases preceding the adrenalectomy by an exploratory laparotomy. The descriptions and weights of the adrenals do not in all cases bear out the statement that they were enlarged. The authors place great importance upon the fuchsinophile reaction of Vines which they claim is a definite evidence of abnormal function. The chapter on the psychologic aspects of the syndrome is interesting but not fully convincing.

In the chapter on biochemistry, a considerable amount of work on the bio-assay of androgens has been performed which would make it appear that in these cases definite increase of androgens is noted. Probably the most important contribution is that of Marrian and Butler who have isolated a new steroid from the urine of bearers of adrenal tumors.

In spite of its shortcomings, this book must be considered a pioneer attempt at investigation of the adrenal cortical syndrome. No one interested in this subject should fail to read it.

—R. T. Frank.

The present widespread interest in the subject of genitoinfectious diseases makes the appearance of this book, *Syphilis, Gonorrhea and the Public Health*¹⁸ by Nelson and Crain, a very timely one. The official positions and the experience of the authors have enabled them to handle the subject in an authoritative and favorable manner. There can be little doubt that the sudden activity in recent months for the control of the diseases discussed has left not only public health workers but physicians and other interested parties far behind in the knowledge of the present status of the treatment and public health aspects of these diseases. The approach to this problem is most excellently set forth in broad general terms in the chapter on Social Hygiene vs. Public Health.

There is a discussion of these two genitoinfectious diseases from a standpoint of diagnosis, treatment, and communicability as well as an excellent chapter on the granulomas. Of particular interest is the section on communicability of syphilis and gonorrhea. The authors state in the section on statistics that there is an evident decline in mortality from various types of syphilis in certain regional areas, but feel that many certificates of death from syphilis have been incorrectly certified.

The fourth part of the book discusses the control of syphilis and gonorrhea, and includes an evaluation of the laws and regulations as at present constituted. The survey of treatment facilities and the necessity for widespread education of the laity, physician, health officers and allied agencies point to the need for complete frankness in regard to the general attitude of the public toward the two diseases. Later on the methods they propose for administration are presented. The method of combining local and state efforts with Federal Public Health Agencies and support is discussed. The authors outline the need for continuance of prophylactic endeavors through social hygiene programs.

The striking results achieved in the Scandinavian countries in the handling of these problems are presented. Suggestions as to how we may utilize their plans in

¹⁸*Syphilis, Gonorrhea and the Public Health*. By Nels A. Nelson, Director, Division Genitoinfectious Diseases, Massachusetts Department of Public Health, and Gladys L. Crain, R. N., Epidemiologist, Division of Genitoinfectious Diseases, Massachusetts Department of Public Health. The Macmillan Company, New York, 1938.

*The Diary of a Surgeon*²⁵ is a lusty, picaresque account of medical conditions in the middle of the eighteenth century. Whether it is actually based on fact, it is impossible for the reviewer to judge, but it has all of the vividness of Defoe or Marryat. It shows the intolerable conditions in the London hospitals of the 18th century, particularly the fatality of childbirth and later takes the reader through a bloody naval battle and an island in the Caribbean infected with yellow fever. It is vivid, coarse, picturesque and fascinating.

—R. T. Frank.

Dr. Sutton offers in this volume on *Physical Diagnosis*²⁶ explicit and detailed instructions in regard to taking a history and making a complete physical examination in any healthy or sick individual. The four cardinal features of such an examination are: inspection, palpation, percussion, and auscultation.

The interesting style in which this book is written deserves special emphasis. This becomes particularly evident in the chapters dealing with the heart and the abdomen. The illustrations throughout the book, several in form of colored plates, greatly enhance the understanding of the reader in regard to many important details of physical examinations for the purpose of exact diagnosis.

All in all this volume represents a noteworthy addition to medical literature.

—Harold Scheff.

On appearance of the first edition of *Progressive Relaxation*,²⁷ in 1929, we described the scope and contents of this most noteworthy contribution to medical literature. It presents a systematic analysis of the neuromuscular states and their significance in medical diagnosis and therapy. Physicians, psychologists and physiologists apparently are evidencing intense interest in this novel problem. Thus it became necessary to prepare a thoroughly revised second edition which embodies all recent work, particularly that of physiologists and psychologists, on reflexes, muscular contraction, sleep, emotion, imagination and other functions. The volume discusses not only the underlying physiologic factors of abnormal muscular states but as well elucidates their connections with various diseases, and describes in detail the methods and procedures by which the desired relaxation and rest actually can be obtained. From this viewpoint alone the book should prove of great practical value to every practitioner of medicine.

—Hugo Ehrenfest.

That this small handbook, *Synopsis of Ano-Rectal Diseases*,²⁸ has reached its fifth edition, is ample evidence that it has met a well-defined need and reflects a growing interest in proctology by the general practitioner.

Various chapters discuss symptoms and their significance, examination of the patient, anesthesia, especially local anesthesia, and details of office treatment. Succeeding chapters discuss particular lesions and their management, although the author has wisely omitted the treatment of the major disturbances of the rectum and colon.

The book is profusely illustrated, particularly with reference to the details of treatment and technic of minor operations. This manual should continue to hold its evident place in the literature of this specialty.

—Philip F. Williams.

²⁵*The Diary of a Surgeon in the Year 1751-1752.* By John Knyveton. Edited by Ernest Gray. 322 pages. D. Appleton-Century Co., New York, 1937.

²⁶*Physical Diagnosis.* By Don C. Sutton, Associate Professor of Medicine, Northwestern University School of Medicine, etc. With 298 Text Illustrations and 8 color Plates. 495 pages. The C. V. Mosby Company, St. Louis, 1937.

²⁷*Progressive Relaxation.* By Edmund Jacobson, A.M., Ph.D., M.D., Laboratory for Clinical Physiology, Chicago. 491 pages. The University of Chicago Press, Chicago, 1938.

²⁸*Synopsis of Ano-Rectal Diseases.* By Louis J. Hirschmann, Professor of Proctology, Wayne University, etc. With 174 text illustrations and 6 color plates. 288 pages. The C. V. Mosby Company, St. Louis, 1937.

In this small brochure, *Twenty-Eight Years of Sterilization in California*,²² are presented the findings of a second study covering 10,000 cases of eugenic sterilization of selected persons in California State Institutions.

Since 1909 California has been systematically enforcing a eugenic sterilization law, and the immediate conclusions of the operation of this law are presented here. The book deals with the method of operation and application of the law in various types of mental disorders, epilepsy and feeble-mindedness. The authors do not feel that sterilization of these individuals has tended to increase promiscuity, and they show by a comparison with divorce rate among normal people that the marriage of sterilized individuals has been quite satisfactory.

The day has passed when eugenic sterilization can be regarded as an experiment. The conclusions of this little booklet prove its success.

—Philip F. Williams.

The 1936 and 1937 series of lectures to the laity established by the New York Academy of Medicine are presented in *Milestones in Medicine*.²³ Seven lectures deal with such varied topics as psychiatry, heredity, leprosy, and glands of internal secretion. These lectures are not at all in a popular style, but are unique in that they are presented as an historical description of the development of the established facts of a particular subject, and the explanation of the sequence of and reasons for evolution of the subject. Dr. Stoddard's lecture on heredity and Dr. Timme's story of the glands of internal secretion are outstanding.

This collection might well be suggested by an obstetrician as a book to be read by his own patients.

—Philip F. Williams.

In these days of dislocated sociologies and recessive finances a book on *The Physician's Business*²⁴ is opportunely published. Dr. Wolf offers a volume which covers the business and practical aspects of medical practice in a clear and simple manner. It is just possible that he might have added one other chapter to this excellent book on the consideration of whether or not a young man should take up medicine as a career.

Beginning with the selection of hospital internship for the recent graduate, he discusses other opportunities than those offered in private practice, and proceeds to the origin, extent, and selection of a specialty. He offers sage advice in the problem of location and speaks words of wisdom on the manner of professional contacts, with practical suggestions to cordial and ethical relationships with colleagues.

Records, both medical and financial, are discussed in detail. There is included a minimum fee schedule of the Industrial Commission of the State of New York as a suggestive basis for fees. Dr. Wolf offers many series of printable directions which may be useful in either general or special practice. The equipment, personnel, and technic of office practice is thoroughly covered. Such intimate matters as income tax, insurance, and other topics, including legal complications and current trends in practice are brought out.

This is an excellent guide to the material aspects of medicine, and it may well be studied by a young physician as he begins his work, or by an older physician who contemplates a change in his location or type of practice.

—Philip F. Williams.

²²*Twenty-Eight Years of Sterilization in California*. By Paul Popenoe, Sc.D., and E. S. Gosney, B.S., LL.B., Pasadena, 1938.

²³*Milestones in Medicine*. Laity lectures of the New York Academy of Medicine. Introduction by James Alexander Miller, M.D. 276 pages. D. Appleton-Century Company, New York, 1938.

²⁴*The Physician's Business*. Practical and Economic Aspects of Medicine. By George D. Wolf, M.D., Attending Oto-Laryngologist, Sydenham Hospital, New York City, etc. Foreword by Harold Rypins, M.D., F.A.C.P. With 57 illustrations, 354 pages. J. B. Lippincott Company, New York, 1938.

In the present edition visceral pain has been made the subject of a separate chapter, and a chapter on vegetative centers of the brain and cord has been added.

The first part of the book deals with a general consideration of the anatomy of the vegetative nervous system, its physiology, pharmacology, and the various phases and theories of cellular activity.

In the second part of the book are discussed the relationship of the vegetative nervous system and symptoms of the visceral disease, and, further, the clinical studies of the viscerogenic reflexes as related to the various systems and organs. It is to be regretted that the work of Cotte has not been taken into consideration in the discussion of the clinical conditions of the urogenital tract. In discussing the inseparability of visceral neurology and endocrinology, separate studies take up the various glands of internal secretion. The author states that no definite relationship between pituitary secretion and nerve stimulation has been shown. This situation differs from that found in two other important organs of internal secretion, adrenal and thyroid, where the activity of the gland is stimulated by the sympathetics.

—Philip F. Williams.

In this small volume, *Wundversorgung und Wundbehandlung*³³ Dr. von Seemen presents a thorough consideration of surgical incisions. The physiology of the healing of such incisions is followed by a discussion of the technique and care of incisions, a short consideration of drainage in relation to wound healing, and the pathologic processes in infected wounds. He describes the relation of physical and chemical disinfection of the skin in relation to wound healing, and presents several graphs to illustrate the relationship between the general physiology of the body to extensive surgery of the surface.

There is a short chapter on the use of electric knives and needles and the healing of wounds so produced. In a brief appendix he lists the various disinfecting, stimulating, and coagulating materials used in his clinic, and a list of the sera used for tetanus, gas edema, and other anaerobic complications.

—Philip F. Williams.

Item

American Board of Obstetrics and Gynecology, Inc.

The next examinations (written and review of case histories) for Group B candidates will be held in various cities of the United States and Canada on Saturday, November 5, 1938, at 2:00 p.m., and on Saturday, February 4, 1939. Application for admission to the written examination scheduled for February 4, 1939, must be filed on an official application form in the office of the Secretary at least sixty days prior to this date (or before December 4, 1938).

The general oral, clinical and pathological examinations for all candidates (Groups A and B) will be conducted by the entire Board, meeting in St. Louis, Missouri, on May 15 and 16, 1939, immediately prior to the annual meeting of the American Medical Association. Application for admission to Group A examinations must be on file in the Secretary's Office before April 1, 1939.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Bldg., Pittsburgh (6), Pa.

The following names were not included in the previous list of candidates certified by the American Board of Obstetrics and Gynecology but received certification at the San Francisco meeting in June, 1938:

GEORGE E. KLEEMAN, JR., Oakland, Calif.

MAURICE L. HORWITZ, Oakland, Calif.

GEORGE W. HEWITT, Los Angeles, Calif.

³³*Wundversorgung und Wundbehandlung*. By Professor Dr. H. v. Seemen, Chirurgische Universitäts-Klinik München. 92 pages. Ferdinand Enke, Stuttgart, 1938.

As the title indicates this volume is written as a *Textbook of Diagnostic Roentgenology*²⁹ chiefly for students.

Illustrations and legends throughout the book are clear. All technical procedures are explicitly set forth in the various chapters, those not frequently employed more briefly. As the outstanding section of this book we consider that dealing with the osseous system. Table of contents and the index are well arranged and for this reason this volume must be regarded not only as a suitable textbook for students but also as a most useful aid for quick reference.

—P. C. Schnoebelen.

This manual on *Approved Laboratory Technic*³⁰ appeared first as a publication of a Committee of the American Society of Clinical Pathologists. In the present edition the technique and methods offered have been approved by a group of 28 collaborators, and include many methods developed, and appraised as of value, during the past seven years. The book covers the field thoroughly, discussing in the first part the general laboratory methods, in the second part the clinical pathology methods, in the third part the bacteriologic, in the fourth part the serologic, and in the fifth and final part the chemical methods. These various methods discussed include all phases of the activities of the general clinical pathologic laboratory as equipment, animals, technique in animal tests, and technique in clinical examinations such as tests of kidney function, stomach contents, exudate and transudates, etc.

An entire chapter deals with the hormonal diagnosis of early pregnancy and the quantitative methods used in the diagnosis of hydatidiform mole and chorio-epithelioma.

This work may be considered an authoritative standard, which should be of value to the obstetrician and gynecologist who is concerned to any extent with the performance of the laboratory examination of his patient.

—Philip F. Williams.

In *Eat and Keep Fit*³¹ the author presents for the lay public a comprehensive discussion of the nature of our food supply. He discusses in simple terms the constituent elements and food values of the various things we eat from the standpoint of why the body needs them and what happens if they are lacking. He gives a common sense presentation of the present status of the vitamins and emphasizes their importance in language easily understood by the laity. There is an excellent chapter on normal diet, and a rational discussion of methods whereby the body weight may be increased or reduced.

In addition, he presents diets illustrating gain and loss values in foods. There are tables which show caloric and constituent values of common foods. The book is well written, the material simply presented, and can be recommended by physicians to those of their patients interested in the subject.

—Philip F. Williams.

Dr. Pottenger has brought out a fifth edition of his book, *Symptoms of Visceral Disease*.³² In recent years clinical interest in this subject has been increased particularly in regard to the visceral nerves as related to angina and vascular disease.

²⁹*Textbook of Diagnostic Roentgenology*. By Lewis J. Friedmann, M.D., Director, Roentgen Ray Department, Bellevue Hospital, etc. With 638 illustrations, 622 pages. D. Appleton-Century Company, Inc., New York, 1937.

³⁰*Approved Laboratory Technic*. By John A. Kolmer, Professor of Medicine, Temple University, etc., and Fred Boerner, Assistant Professor of Bacteriology, School of Medicine and Graduate School of Medicine, University of Pennsylvania, etc. Edition 2, rewritten, revised, and reset, with 12 plates and 320 illustrations in the text, 893 pages. D. Appleton-Century Co., New York, 1938.

³¹*Eat and Keep Fit*. Scientific Secrets of Diet. By Jacob Buckstein, M.D., Consulting Physician in Disease of the Stomach to Central Islip Hospital, etc. 128 pages. Emerson Books, Inc., New York, 1938.

³²*Symptoms of Visceral Disease*. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine. By Francis Marion Pottenger, M.D., Medical Director, Pottenger Sanatorium for Disease of the Chest; Professor of Clinical Medicine, University of Southern California, etc. Edition 5, with 57 text illustrations and 10 color plates, 442 pages. The C. V. Mosby Company, St. Louis, 1938.

furthermore, the service in internal medicine may be limited to metabolic diseases and the surgical experience may be largely limited to abdominal work, the training the intern receives lacks much of what should be expected of the fifth year. It may be possible for an intern to get a better training on a rotating service in a less famous hospital in which the work is more general and less highly specialized. When the work offered an intern by any hospital is not general enough, the medical colleges should remove such an institution from their lists of hospitals approved for the fifth or required year of internship. There are plenty of hospitals with high standards of efficiency in which the nature of the work done is general enough to give interns a broad and varied training for their fifth year, and only such institutions should be approved for this work.

Special hospitals, teaching hospitals, and such institutions where the nature of the patient body or the reputations of the various staff members are such as to make for high degrees of specialization become available at once for the training of specialists, by replacement of the fifth year internships with special internships and residencies. You are looking for methods of measurement to determine goals of achievement and are confronted by the fact that your measuring stick must be flexible instead of rigid and unyielding. There is no inflexible standard for measuring professional ability. In your own acquaintanceships you know self-made men who excel the products of long training, yet since it is well known that training is generally requisite for competency, a minimum standard seems advisable. The length of residency in an institution required for certification would vary with the opportunities offered, but in my mind should not be longer than three years. This length of time skillfully directed should amply train an aspirant in every phase of his specialty and prepare him for a start in the practice of his art. To remain too long in one institution is a real danger for a young man. It is too likely to fix his ideas and limit his development. Too long a period of training in one institution produces the man anxious to tell of his institution's methods of treatment instead of the eager seeker after new methods for his own improvement. This residency period should be broad in its experience and active to the extreme. There is more than wishing to acquiring proficiency. Contemplation does not develop diagnostic acumen, nor philosophic discussion surgical technique. Clinical material should be abundant and responsibility for its management developed. Thorough training in the anatomy and pathology of the specialty is of prime importance. Though a man expects to be an obstetrician he should during these years have enough training in gynecology so that he may be a safe operator in obstetrics when the occasion arises, since indicated obstetric operations do not occur with frequency enough to keep his surgical technique fit. Also now that services in obstetrics and gynecology are being more commonly combined he should prepare himself for that possible contingency in his own future and have a good basic training in gynecology. Equally so should the aspirant in gynecology have, during these hospital years, a good training in ob-

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Sixty-Third Annual Meeting, May 30 to June 1, 1938

Dr. N. Sproat Heaney, Presiding

PRESIDENTIAL ADDRESS*

N. SPROAT HEANEY, M.D., CHICAGO, ILL.

AT THIS time, when considerable thought is being devoted by the medical profession to the licensing of specialists in the various branches of medicine, it may not be considered amiss for the President of the American Gynecological Society to express a few thoughts relative to the training of specialists in obstetrics and gynecology.

Now that formulas for preliminary training are being outlined and published, it becomes apparent from the large number of applications for residencies being received everywhere, that great care must be taken if sufficient suitable positions are to be supplied. At the present time, chiefly in the larger cities and particularly in connection with medical schools, there are a large number of hospitals which accept interns for their fifth year's work where the practice of the hospital is so specialized or the rotation of the internship is so restricted that the intern does not get a good general training. The medical colleges should be stricter in their certification of hospitals for the required or fifth year, and should exact that the internship should be widely rotating and general to the extreme in the nature of the training given. Six months' service in internal medicine and six months in general surgery is quite commonly accepted as a substitute for the required internship. This would not seem comprehensive enough for entering general practice in which so much of the practitioner's work has to do with obstetrics and the attention of sick children, nor is it a broad enough experience to use as the base upon which to build a training in some specialty. When,

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

Or this fourth year might be spent in a laboratory of investigation where research work is done. There is a move on foot to require research work of every candidate for specialization. This is laudable if practicable. Progress in medicine can only be expected through investigation. The man with a research type of mind can best evaluate the clinical application of new discoveries, but shall we require this as a necessary qualification for licensure? If so, where will all these candidates find qualified masters to teach them, or can a few teachers be expected to turn to mass production? What constitutes research work in Gynecology and Obstetrics? In History it consists in seeking the original historical data in archives and libraries. In English an investigator may gain repute by his discovery of new unpublished bits from Chaucer. In our specialty much acclaim is given him who works in physiology, chemistry, or physics. Once reputations were firmly established by researches into the morphology of tissues. Not much credit is given to the student of histology today as being engaged in research work, yet I must draw to your attention that in my opinion the painstaking studies of Sampson, resulting in our knowledge of the nature and behavior of endometriosis, has had far more effect on the practice of gynecology today than any other single bit of research work done during the same period in obstetrics and gynecology, whether test tube and guinea pig were used or not. So before research or investigation is required real research and investigation must be defined. One thing which should not be lost sight of is that the various boards of licensure are trying to establish indices for the fitness of candidates to practice their specialties; in our specialty, for example, whether they are competent to be declared "Approved for the practice of gynecology and obstetrics." What has that to do with research work? This board is not qualifying men for heads of departments in medical colleges. You cannot hope to regulate the production of leaders. Leaders cannot be kept down, they will develop in spite of regulation. You can hope only to develop good followers of which there are not enough. At present I believe that a great deal of self-deception exists among us as to the real value of the research work we engage in, both as to its value to us as individuals and the progress of medicine at large. He who has research ability is fortunate, and this ability should be fostered and encouraged and I may say steadied and not allowed to go off half-cocked to be corrected in a subsequent arbeit. In his fourth year a young specialist should be full of problems demanding solution, if he has a research mind, and a year under a recognized investigator in a physiological, chemical, or physical laboratory will teach him exact methods. The proper teacher will help him with problems concerning his specialty, and if he is a good teacher he will determine whether the aspirant has the mind to prosecute research work or should end his self-deception. At any rate research work must not be a fetish and should be an addition to adequate clinical and technical training. It should not, by any stretch of the imagination, be considered a substitute.

After the third hospital year, the aspirant may be taken into a specialist's office as an assistant for further training. This is not only

stetrics. Certainly the gynecologist should know the physiology of the genitalia, which is childbearing, and studying obstetrics is essential to his training. The stamp of the obstetrician is seen in the character of every gynecologist's work who has been trained in both branches. Furthermore, in practice the ability to do obstetrics will enable the novice quickly to establish his competence, for obstetrics comes easily to a young man while gynecology is coy and demands more evidence of age. Thus a young gynecologist may early practice his specialty and not make excursions into the general surgical field in which he is untrained in order to earn a livelihood, nor slump into general practice for which he is equally unsuited. Finally in his degenerative years the man thus trained may leave his obstetrics to physically able young men and avert untimely death by retiring to gynecology, where he may be active and efficient with a minimum of effort, not only to his own benefit but that of the obstetric and gynecologic cases which demand his attention.

After three years, sometimes sooner, he should leave the hospital of his special training and seek some other connection. Nothing is so illuminating as a change of chiefs. The next year he might well spend in travel and in taking special courses to make up the deficiencies in his training. There can be no question of the great benefit many of us obtained from our years in Berlin, Dublin, London, Edinburgh, or Vienna, years ago before war and near war made these centers difficult for study. We returned with new ideas, new ambitions, and new ideals. The effect of this training on American obstetrics and gynecology is still felt today. Now that such traveling is impractical and unsatisfactory for many reasons, we should encourage young specialists to travel more among the American clinics which are the equal of any abroad. In one center he would find much to stimulate him in investigation, in another he would find an entirely new attitude toward clinical problems which had been satisfactorily settled as far as his previous training had led him to believe. We should not be so satisfied with our own methods and our own technique that we do not encourage our young men to visit others where possibly better approaches to the attack on disease may be employed. An impressive teacher may so imbue a student with his beliefs and methods that the student feels no urge to seek further fields for truth, and inbreeding results. There seems something innate in the active surgical teacher which gives the impression that all truth rests in him. It might not be advisable to disabuse the minds of patients, nurses, and secretaries regarding the fallacy of this created opinion, but we really owe it to our own assistants to rob them of this delusion, so that they in turn may not be bound by our own limitations. They should visit other centers, seek knowledge elsewhere, and thereby lessen the chances of their not excelling their chiefs. Many of us in charge of large clinics have discarded every operative procedure which we once employed and have established new technique, based upon ideas picked up here and there while visiting elsewhere.

in practice for himself, is given a position on the staff of the hospital and on the teaching staff of the medical college. Each of these graduates from my office is assured of a private practice in his specialty out of my own clientele, but this pruning has never injured the parent practice which has endured both the depression and so far the recession. In this way one may make up the deficiencies of insufficient institutional positions both to the progress of obstetrics and gynecology and to one's own satisfaction.

Surgery is defined as that branch of the healing art which resorts to manual operations or mechanical appliances for the treatment of injuries, deformities, or morbid conditions. Surgery is an art and dexterity and proficiency in it come only through much training and hard application, and for the acquisition of this art there can be no substitute for a large experience. Artists and musicians are content to spend long hours daily in gruelling training in order to obtain manual dexterity and supple action. Acrobats and prestidigitators perform the same act daily for hours to train the muscle sense in order that they may do their particular stunts with the most exacting precision. The tap dancer and knife tosser perform their feats, not through a gift bestowed upon them, but accomplish the acts which astound us only after months and years of exacting training. These artists stake their reputations and often their lives on their sheer ability. They strive to excel in their respective arts and their only hope is to amuse us and thereby earn their competence. We deal in human lives. Quick judgment may be based on temperament but its chief support is experience—without experience there is no basis for judgment. Operative dexterity is an asset best appreciated when dealing with the poor operative risk. Many people die from operations who might live were the operator a little more skillful, a little more experienced. These facts cannot be denied. Why, then, are we so casual about our skill, so inclined to disparage technique and why do we try to substitute something else for this indispensable attainment?

In the last analysis examinations for licensure have not as yet been devised which will indicate a candidate's real ability, whether he is an obstetrician and gynecologist of judgment and experience. Were he able to demonstrate that fact he has passed beyond the need of licensure, he has arrived.

helpful to the chief but can be made of the greatest value in the training of the younger man. In the hospital the resident has seen chiefly the seriously sick, or at least those requiring hospitalization. In an office or dispensary practice he sees, in addition, the beginnings of disease and finds that many applicants for medical relief need only the assurance that nothing ails them to obtain that relief. An assistant should be chosen not because he is affable and likable but because he will make an able successor. That he may too soon become a successor is the fear which closes this valuable avenue of training to many. Nothing is so horrendous in its results as selecting assistants because they are good "yes men." How often the mantle of succession to a professorship has been placed on the shoulders of such a "yes man" grown older, to the detriment of the progress of medicine.

Years ago I became aware of the fact that if I were to train teachers for my staff at the college and hospital I would have to do it through accepting assistants in my office, for the teaching and clinical beds at my disposal were too few to train adequately the men under me in a reasonable time. I remodeled my office so that a large number of patients could be attended. Fixed fees were abandoned and all who wished attention were made welcome. As largely as possible the active care of patient was turned over to the ministrations of my assistants and my own attention was given to the supervision of their work and the treatment of the most exacting or complicated cases. Obstetric and gynecologic cases were handled alike and the fees of the poor and of persons with limited means were largely a matter of their own decision. The rich came along with the poor, were charged abundantly, and were happy in most instances to pay the fees exacted, because they had before them the visible reasons for variations in fees. Assistants were taken on for a period of three years. In order that the assistants' activities could be controlled and their time best occupied for their own learning and advancement, flat salaries were paid for the disposition of all their time and efforts, and the salaries were increased for each year of service. The salaries were sufficiently ample that at the end of three years the assistant could pay for a year's study abroad. When this calculation failed I loaned them enough money to make up the deficiency. In this way I built up a large practice to the satisfaction of all concerned, and today I have the records of over 11,000 admissions to my office. When it is taken into consideration that for the first several years the work was largely obstetric and that many of these patients had several children, the amount of work done was considerable. When it is further stated that this does not include dispensary activities pursued at the same time, nor clinical patients or those seen only at the hospital, nor consultations on other services in our own hospital or other hospitals, except when occasionally the patient would return to the office, it becomes apparent that our experience was a rich one. After returning from his foreign training the assistant goes into private practice on his own responsibility. He is allowed to notify such of my clientele as were earlier turned over to him for his attention that he is

level in five to twenty-five minutes. Furthermore, with electrodes similarly placed, they were unable to obtain anything resembling this type of potential change by dropping follicular fluid into the peritoneal cavity, by injuring the ovarian cortex, or by puncture of other abdominal organs. However artificial rupture of a follicle accomplished without injury to the ovary produced an increase in potential difference like that observed with normal ovulation. In 1937, Burr, Musselman, Barton, and Kelly,⁷ applying electrodes in the same places, obtained marked changes in potential in a human female at the time when, as shown by subsequent laparotomy, ovulation could have occurred. Rock, Reboul, and Wiggers⁸ also reported one similar experiment. In both of these experiments during a period of several hours preceding the moment of greatest potential difference, suggesting by analogy the moment of follicular rupture, there was recorded a slow increase of potential which warned of the approaching event. Substantiation of these two phenomena, a maturation sign and a rupture sign, would have great practical significance.

In a series of experiments on normal, ovariectomized and hypophysectomized rats, Rogers⁹ recorded an increase of potential caused not by changes in the ovary or in the vagina, but by the more generalized phenomenon called *estrus*, and showed that the acme of this potential difference is reached just before the animal passes out of estrus. This electrical disturbance occurs not within five to twenty-five minutes, like the one observed in the rabbit, but the complete rise and fall of the potential takes about fifteen hours.

INDICATIONS OF OVULATION

A major difficulty and fearsome hazard in interpreting the curves of potential changes obtained in human experiments comes from our lack of any other reliable sign of ovulation to which we might refer the observed change in potential. An unpublished study of some 600 human vaginal smears in 1935 taught us that ovulation could not be accurately detected in this way. Rubenstein's discovery of a temperature drop during the hours of follicular maturation and rupture has only recently come to our notice.¹⁰ "Mittelschmerz" we depended on in one allegedly infallible patient and found it of unjustly exaggerated repute. Our resources have not permitted the arduous and time-consuming work incident to continuous hormonal studies.

We planned our experiments therefore to utilize women who needed laparotomy for a condition which did not entail any significant ovarian pathology or dysfunction, and to make our observations between the seventeenth and eleventh days (inclusive) before any likely subsequent menstruation. These dates were computed on the basis of the recent catamenial history. Excluding the controls, and with the exception of one ovulating case, all the women on whom dependable readings were obtained were subjected to laparotomy soon after suggestive changes in potential were recognized, and the condition of their ovaries or ova was used to estimate the time of ovulation. While this means of dating ovulation from the gross or even microscopic findings in the corpus luteum, or from the condition of ova, is inaccurate to an appreciable degree, we believe it to be the most satisfactory method at present.

In six patients examination of the ovaries was made within thirty hours and in one case fifty-one hours after the electrical change. In another patient the curve of ovulation was not recognized until more

ELECTRICAL CHANGES ASSOCIATED WITH HUMAN OVULATION*

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BOSTON, MASS.

(From the Fertility Clinic, Free Hospital for Women, and the Department of Physiology, Harvard Medical School)

STUDIES of mammalian ova (Pincus;¹ Allen, Pratt, Newell and Bland;² Young and Blandau³) justify the conclusion that, like other cells of the body, the mature fertilizable ovum is dynamic, and when it has reached its limit of autogenous growth, it must be fertilized within a short time or perish. The exact limit of this "short time" has not been determined, but by analogy to data obtained particularly on the rabbit (Pincus)¹ and on the monkey (Hartman),⁴ we believe that it is of the order of hours and not days. Spermatozoa, too, seem to have but a short functional span, limited perhaps not only by length of life, but by their dissemination. Though one spermatozoon may fertilize, the assistance of many is normally essential. Knowledge then of just which hours during any given ovarian cycle the ovum is free and susceptible to spermatozoa, would be of profound value to the rational control of human fertility. Various statistical studies correlating menstruation with coitus and fertility have confirmed the conclusion drawn from endocrine and anatomic studies that ovulation normally occurs in a strictly limited time relation to a subsequent menstruation. This much is exceedingly helpful, but the duration of ovulation time thus indicated is still a matter of four or five days, during only a few hours of which the ovum is actually susceptible to fertilization; and still more unsatisfactory is the fact that the date of the subsequent menstruation from which we may estimate ovulation time is predictable only within a wide range of several days or even weeks.

This report presents experiments designed to determine more directly the exact moment when the mature human ovum is liberated from the follicle.

REVIEW OF LITERATURE

In rabbits, Burr, Hill, and Allen⁵ (1935) detected by means of a vacuum tube potentiometer a marked difference of potential between a suprapubic and a vaginal electrode when each ovulation occurred. Reboul, Friedgood, and Davis⁶ (1937), employing a similar technique, with the abdomen open and the ovaries under inspection, found that the peak of the potential difference was reached at about the moment of follicle rupture. Usually the potential difference passed through a maximum of 6 to 10 mv. within thirty seconds and returned gradually to its former

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

This investigation was aided in part by the Permanent Charity Fund of the Harvard Medical School, by the National Committee on Maternal Health, and by a special grant from the American Academy of Arts and Sciences.

young males, two women past the menopause, and one woman in the nonovulatory phase of her cycle.

CASE 1.—Mrs. J. C., aged 34, had had 7 pregnancies.

Diagnosis: Dysmenorrhea. Prolapse. *Pelvic Examination:* Slight vaginal relaxation. Lacerated, eroded cervix. Fundus normal size, forward, freely movable. Vaults negative. *Range of Cycle Lengths:* 26 to 30 days. *Last Menstrual Period:* September 7. *Estimated Ovulation Time:* September 17 through September 25.

Procedure: On September 17 at 2:15 P.M. the salt-bridge electrodes were attached; one was inserted in the vagina, and one placed on the abdomen; the latter served as reference electrode. The vacuum tube potentiometer was employed, and readings of potential changes were taken at five- or six-minute intervals from the deflections of a galvanometer connected to the vacuum tube potentiometer. The experiment ended at 9 A.M. on September 19.

Description of Curve: Due to an error in recording, the data obtained previous to September 18 had to be discarded. On September 18 the record showed a base-line that remained steady within ± 2 mv., until at 9:45 P.M. the potential, then at about 1 mv., suddenly rose, and by the end of two hours (11:46 P.M.) it had attained a peak of nearly 10 mv. (i.e., an increase which was about five times the maximum of the oscillations on the base line).^{*} Then for about three-fourths of an hour the potential remained at a fairly high level. At the end of this period (12:24 A.M.), it dropped suddenly to the original base line level. Unfortunately polarity was not determined here. The peak of the change thus occurred on the twelfth day of Mrs. C.'s cycle.

Operative Findings: Operation at 11 A.M. on September 19 (i.e., twelve hours after the peak had been reached) revealed a freshly ruptured follicle in the right ovary with early corpus luteum formation. This was photographed before fixation. No ovum was recovered from the tubes which were irrigated in situ. Microscopic examination of the corpus luteum showed an open stigma; theca about 24 cells deep; granulosa layer absent; extravasation of red blood cells in small masses among thecal cells.

The endometrium was in the late proliferative stage.

CASE 2.—Mrs. A. F., aged 24, had had 2 pregnancies and 2 abortions.

Diagnosis: Lacerated perineum. Cystocele. Prolapsus uteri. *Range of Cycle Lengths:* 28 days. *Last Menstrual Period:* September 28. *Estimated Ovulation Time:* October 10 through October 14.

Procedure: On October 9 (2 P.M.) the electrodes were applied. A glass-covered vaginal (saline-AgCl-Ag) and a glass-covered abdominal (saline-AgCl-Ag) electrode were used here, the abdominal serving as reference electrode. At noon on October 10 a new abdominal electrode covered by a rubber cup was attached. Voltage changes were usually measured potentiometrically at fifteen-minute intervals.

Description of Curve: For about twenty-four hours the vaginal electrode was slightly negative to the reference electrode; the base line showed oscillations as high as ± 5 mv.

On October 10 (2 P.M.), the vaginal electrode became positive to the reference electrode. The potential increased steadily until at the end of six hours it had attained a peak value of +30 mv. Then in the next twelve hours the potential decreased slowly until it reached a level of +10 mv. At about this time the record was stopped (October 11, 10 A.M.). The peak thus occurred at 8 P.M. on October 10; i.e., on the thirteenth day of her cycle.

Operative Findings: At operation on October 11 at 11:30 A.M. (about sixteen hours after the peak had been attained) a recently ruptured follicle with open stigma was discovered in the right ovary. Microscopic examination revealed the following: The luteinized thecal layer was 12-20 cells deep and contained many vacuoles and

^{*}In this first experiment there is some doubt as to the correctness of the absolute values indicated, as the calibration of the apparatus was doubtful. The relative values are as given in the text.

than eight days had elapsed.* Operation then showed endometrial and corpus luteum development which, according to present standards, placed ovulation about eight days before operation. One patient was not operated upon but menstruated on the fifteenth day following the observed increase in potential. Such a time relationship between ovulation and menstruation has the sanction of current theory.

TECHNIQUE

Electrodes.—Our methods of electrode contact with two points arbitrarily chosen in the possible field of electrical disturbance, as well as our method of recording differences in the potentials of these two points, have been modified in several ways since the original report.

In our earlier experiments the electrodes consisted of wicks wet with normal saline solution and connected by salt-bridges to silver-silver chloride electrodes which in turn were connected by insulated cables to the vacuum-tube potentiometer. As the contact wicks or the salt-bridges dried too easily we later used a jelly made with agar-agar and normal salt solution into which the silver-silver chloride electrodes were imbedded (Rock, Reboul, and Wiggers⁸). At the present time we use electrodes made by filling a porous rubber cup with salt-agar jelly to which is added a little glycerin to prevent drying. Imbedded in this jelly is a small zinc plate which is connected directly to the recorder. The rubber cups are inverted and firmly applied to the patient's skin by means of paste washed off by xylol from ordinary adhesive tape.

Recording Apparatus.—For measurement of potential changes we first used a vacuum tube potentiometer similar to that of Burr, Lane, and Nims,¹¹ and later a different type which has been described by Reboul, Davis, and Friedgood.⁶ The changes of potential thus detected were recorded by means of a galvanometer and a slow moving camera. Later when it was discovered that the differences of potential were of such magnitude as to permit of a less delicate mechanism, we used an ordinary battery operated slide-wire potentiometer to balance the differences of potential. The slide-wire used was identical to that contained in the Leeds and Northrup Type K potentiometer. At intervals of from five to fifteen minutes we made readings of the voltage necessary to bring a sensitive galvanometer to its zero position. These readings were independent of the external resistance to a sufficient extent.

Since this method proved satisfactory we then used a Leeds and Northrup multi-point recording potentiometer (Micromax recorder). This works on the potentiometer principle, and also provides an automatic record for 6 different circuits every twelve minutes; or, if all leads are used in one circuit, every two minutes. Hence, records may be taken simultaneously on several patients or from different pairs of electrodes on the same patient. In the later experiments we were thus able to use two pairs of electrodes; one pair low in the pelvis, and one pair higher up, and a third circuit recording the difference of potential between the two right electrodes of these two pairs. Three of the 6 circuits provided by the recorder were thus used, and a record obtained from each of these every six minutes. On this apparatus the control experiments were made (with the exception of Experiment 1 on Mr. A. U. where the manually operated potentiometer was employed).

EXPERIMENTAL

Following are the details of nine experiments made on women with normally functioning ovaries during their estimated ovulation time. As controls for the above, observations are presented on three healthy

*Until one is able to determine the magnitude of base line oscillations, it is impossible to recognize the characteristic ovulation curve. (See under experimental results, I, a, page 741.)

several adjacent ones. The ovum obtained from the follicle in the right ovary, as well as two of the ova recovered from the left ovary, were not sufficiently atretic to be unattractive to spermatozoa.

Microscopic examination revealed a young corpus luteum, the theca interna of which had a depth of 10 to 20 cells. Among these, extravasated blood cells appeared in many small spaces as yet unlined by endothelium. However in the outer layer of this luteinized theca centripetal capillaries were apparent. The granulosa layer was absent. The immaturity of the corpus luteum, as well as the absence of degenerative changes in the ova of other follicles, implied, we believe, that ovulation had occurred not more than twenty-four hours before operation.

The endometrium was in the early secretory stage.

CASE 5.—Mrs. M. G., aged 27, had had no pregnancies.

Complaint: Sterility. *Diagnosis:* Bilateral tubal occlusion. *Pelvic Examination:* Normal introitus and vagina. Cervix of normal size, shape and position; movable. Fundus of normal size, anterior, movable. Slight thickening in left vault. Right vault negative. Very slight first degree prolapse. Mucoid cervical discharge. *Range of Cycle Lengths:* 27 to 29 days. *Last Menstrual Period:* October 5. *Estimated Ovulation Time:* October 16 through October 22.

Procedure: On the morning of October 16 a rubber-covered electrode (saline-AgCl-Ag) was applied on the abdomen, and a glass-covered electrode (saline-AgCl-Ag) was inserted in the vagina, the abdominal serving as reference electrode. The first reading was taken at 11:05 A.M. and subsequent readings usually at fifteen-minute intervals. The experiment ended at 5:30 P.M. on October 19.

Description of Curve: This curve is characterized by a very rapid potential increase of 24 mv. in the negative direction beginning on October 18 at 5:30 A.M. The potential remained high for about eight hours after which it gradually returned in nineteen hours to the original base line which previously had shown oscillations not greater than ± 5 mv. The peak here thus took place on the fourteenth day of the cycle.

Operative Findings: Operation at 10 A.M. on October 20 (fifty-one hours after the peak had been attained) disclosed in the right ovary one freshly ruptured follicle with open stigma. Microscopic examination showed a luteal layer about 20 cells deep which was vacuolated and infiltrated with extravasated blood. Many dislodged granulosa or theca-lutein cells were free in the coagulum.

The endometrium was in the late proliferative phase.

CASE 6.—Mrs. H. G., aged 27, had had no pregnancies.

Complaint: Sterility. *Pelvic Examination:* Normal except for hypersecretion of cervical fluid. *Range of Cycle Lengths:* 25 to 31 days. *Last Menstrual Period:* November 5. *Estimated Ovulation Time:* November 14 through November 24.

Procedure: On November 15 (12 Noon) 2 pairs of surface electrodes (saline-agar-zinc plate) were applied. The left electrodes served as reference electrodes in both pairs. Manual potentiometric determinations of voltage were recorded at five- and ten-minute intervals alternately; i.e., a reading was obtained for each circuit every fifteen minutes. The experiment ended at 4 P.M. on November 17.

Description of Curve: Between 3 and 4 P.M. on November 15 (i.e., within one hour) the right lower electrode became about 40 mv. more positive with respect to the left electrode, and then returned very slowly to its original potential in about thirty-six hours.

This change was not reflected on the upper pair which showed a base line steady within ± 6 mv. and shifting slowly from a zero position to a slight positivity.

This patient was not operated upon, but she did start to menstruate on November 30, the fifteenth day after the peak was reached. This menstrual period occurred on the twenty-sixth day of her cycle. The peak had been observed on the tenth day.

In the following three experiments potential changes very similar to those described above were obtained yet ovulation had not occurred.

CASE 7.—Mrs. H. C., aged 37, had had 4 pregnancies and 1 abortion.

Diagnosis: Rectocele. Cystocele. Prolapsus uteri. *Range of Cycle Lengths:* 28 to 30 days. *Last Menstrual Period:* November 1. *Estimated Ovulation Time:* November 12 through November 18.

clumps of extravasated erythrocytes. The coagulum, which also contained many free red cells, lay in contact with the thecal layer. There was no granulosa or limiting membrane.

CASE 3.—Mrs. H. D., aged 37, had had 2 pregnancies.

Diagnosis: Lacerated perineum with cystocele and prolapsus uteri. *Range of Cycle Lengths:* 26 to 32 days. *Last Menstrual Period:* October 12. *Estimated Ovulation Time:* October 22 through November 1.

Procedure: On October 23 (1 P.M.) one pair of surface electrodes (saline-agar-zinc plate) and one pair of vaginal-abdominal electrodes (saline-AgCl-Ag) were applied. Potentiometric determinations of the voltage were recorded at seven- and eight-minute intervals alternately; i.e., a reading was obtained for each circuit every fifteen minutes. The experiment ended on November 1 (8 A.M.).

Description of Curve: On October 23 (5 P.M.) the right surface electrode showed a steady increase in the positive direction with respect to the left electrode until at the end of four hours it had attained a peak value (9 P.M.). The total increase amounted to about 24 mv. Then began a rapid decrease of potential during two hours followed by moderate fluctuations for about ten hours after which it returned to the initial value. (This change in the surface curve closely resembles the curves obtained in Cases 1 and 2.) Throughout the rest of the experiment the base line remained steady within ± 5 mv. and no other characteristic changes were observed. The peak thus occurred on the twelfth day of her cycle.

On the abdominal-vaginal circuit the base line remained constant (within ± 5 mv.) and no typical fluctuations were noted.

Operative Findings: Laparotomy performed at 12 Noon on November 1 (i.e., eight days and fifteen hours after the peak had been reached) revealed the presence of an old corpus luteum in the left ovary. On section this proved to consist of solid cellular folds. The coagulum appeared to be undergoing fibrosis.

The endometrium was in a well-advanced secretory stage. In the convoluted and saw-toothed glands the epithelium was characteristic of the beginning of the final week of the cycle. The nuclei were basal, and the supranuclear cytoplasm was vacuolated and fragmented. The stroma was moderately edematous except in those areas where the cells were enlarged by a marked increase of cytoplasm. A cellular picture of this type has already been shown to be characteristic of progestin influence over a period of about nine days.¹² The corpus luteum, too, as noted above, was mature. The curve described was obtained on the ninth day preceding operation.

CASE 4.—Miss T. C., aged 21.

Complaint: Dysmenorrhea. *Pelvic Examination:* Nulliparous vagina. Cervix, not lacerated or everted, pointed directly anterior. Fundus of normal size; ante-flexed and deeply retrocessed. Vaults negative. *Diagnosis:* Essential dysmenorrhea. *Range of Cycle Lengths:* 25 to 30 days. *Last Menstrual Period:* October 29. *Estimated Ovulation Time:* November 7 through November 16.

Procedure: On November 8 (2 P.M.) the electrodes were attached. These consisted of one pair of surface electrodes (agar-saline-zinc plate) placed low in the groins, the reference electrode being on the left side. Voltage changes were read by the null potentiometric method at fifteen-minute intervals.

Description of Curve: For the first seven days there was no significant change. During the early half of the week, however, the curve showed slow cyclic oscillations of period one day and of amplitude about 16 mv. On November 15 at around 12 midnight there was a sudden rise from the base line to a value above +80 mv.* The potential remained at this level for about five minutes. It then dropped within an hour to +24 mv. where it stayed constant for six hours. Soon afterward the record was stopped (10 A.M., November 16). The peak here occurred on the eighteenth day of the cycle.

Operative Findings: At operation on November 16 (12 Noon), twelve hours after the peak had been reached, there were recovered from the right ovary a young corpus luteum and one well-developed follicle, and from the left ovary one large follicle and

*Eighty millivolts are the limit of the potentiometer scale.

CASE 9.—Mrs. C. W., aged 33, had had one pregnancy.

Diagnosis: Inguinal hernia. Retroversion. Ovarian cyst. *Range of Cycle Lengths:* 25 to 28 days. *Last Menstrual Period:* September 29. *Estimated Ovulation Time:* October 8 through October 15.

Procedure: This patient was tested from 12 noon on October 6 through 7:15 A.M. on October 9. The electrodes were similar to those used in Case 5; i.e., a rubber-covered saline-AgCl-Ag electrode was applied to the abdomen (reference electrode), and a glass-covered saline-AgCl-Ag electrode was inserted into the vagina. Readings were taken usually at fifteen-minute intervals.

Description of Curve: No base line was obtained for the first twenty-four hours, but a continuous drift occurred; i.e., the electrode which was 20 mv. negative to the reference electrode became 12 mv. positive. Then for the next twelve hours the record was relatively flat with changes in base line no greater than ± 5 mv. At 1 A.M. on October 8 the vaginal electrode became strongly negative to the reference electrode, a change of 25 mv. which took place in about three hours. After this followed a period of great irregularity (oscillations of ± 10 mv.) which might have been due to defects of technique or electrode difficulties. The curve then returned to the first positive level which it attained twenty-four hours after the beginning of the change. The peak thus occurred at 4:30 A.M. on October 8, the tenth day of the cycle.

Operative Findings: At operation on October 9 at 10:30 A.M. (thirty hours following the peak of the curve), a mature follicle which had recently suffered atresia was found in the right ovary. Microscopic examination of this follicle revealed the presence of a well-developed granulosa layer in which beginning degeneration was evidenced by diminution in the size of the marginal cells and their increased affinity for stain. From this follicle was obtained a slightly elliptical ovum which was surrounded by granulosa cells and was not attractive to spermatozoa.

To summarize then: in ten satisfactory experiments (one reported in a previous paper⁸) similar potential changes were observed. Seven of these were associated with ovulation; three of them were associated with maturation of follicles, which, however, had not ruptured.

CONTROLS

In the six control experiments outlined below, the following subjects were tested: (A) 3 healthy young males (control Cases 1, 2, and 3); and (B) 2 women past the menopause (control Cases 4 and 6), and one woman in the nonovulating phase of her cycle (control Case 5).

In all control experiments two pairs of surface electrodes (saline-agar-zinc plate) were used, one pair being placed just above the symphysis, and one pair just below the umbilicus. In the first experiment on control Case 1 (Mr. A. U.) the manual potentiometric method of measuring potentials was employed. In all subsequent control experiments the Micromax recorder was used.

A. Male Controls.—CONTROL CASE 1.—Mr. A. U.

Experiment 1: This experiment lasted from December 5 to December 6. The record showed a fairly steady base line (with fluctuations not greater than ± 8 mv. during the day, and ± 4 mv. during the night). There were some slow undulations occurring at mealtimes which were more marked on the upper circuit. These never exceeded ± 5 mv. on the lower circuit.

Experiment 2: A second test was made on this subject (December 27 and 28). Here the record was a little more unsteady, showing slow changes in base line of ± 10 mv. during the day and ± 4 mv. during the night. Again, as in Experiment 1 on this subject, changes associated with periods of digestive activity were recorded on the upper circuit. This time these were as large as ± 20 or 30 mv.

CONTROL CASE 2.—Mr. D. G.

This experiment ran from December 28 (11 A.M.) to December 29 (5 A.M.). Throughout a period of eighteen hours the record was remarkably steady except for a short episode during which changes were made in the machine by the operator.

Procedure: On November 13 (11 A.M.) the electrodes were attached. These consisted of one pair of surface electrodes, placed low in the groins (saline-agar-zinc plate), the reference electrode being on the left; and one pair of glass-covered vaginal-abdominal electrodes of the salt-bridge type referred to previously, the abdominal serving as reference electrode. Manual potentiometric determinations of voltage were recorded alternatively at five- and ten-minute intervals; a reading was thus obtained for each circuit every fifteen minutes. The experiment ended on November 14 at 9 A.M.

Description of Curve: On November 13, two hours after the experiment was started, there was a sudden change in potential difference from +10 mv. at 1 P.M. to -24 mv. at 4 P.M. under the right surface electrode. Near this level it remained for about twelve hours. The potential difference then gradually diminished to -10 mv. At this time the record was stopped.

The vaginal electrode, which was slightly positive (5 mv.) at 1 P.M. (November 13), became slightly negative by about 10 mv. during the next two hours and then slowly returned to a positive level of +12 mv. where it remained steady for a period of ten hours. The peak of negativity was synchronous with the maximum change over the right surface electrode, which, as mentioned above, was one of 34 mv. in the negative direction. The peak here occurred on the thirteenth day of the cycle.

Operative Findings: At operation on November 14 (11 A.M.), nineteen hours after the peak had been reached, one mature *unruptured* follicle was recovered from the left ovary and this contained an egg which in vitro vigorously attracted spermatozoa. On microscopic examination the wall of this follicle showed a fair degree of luteinization of the theca interna. The behavior of the ovum and the condition of the follicle wall strongly suggested that ovulation was imminent.

The endometrium was in the late proliferative stage.

CASE 8.—Mrs. M. M., aged 21, had had no pregnancies.

Complaint: Sterility. *Dysmenorrhea.* *Diagnosis:* Pelvic inflammatory disease. Adherent retroversion. *Range of Cycle Lengths:* 28 to 30 days. *Last Menstrual Period:* November 7. *Estimated Ovulation Time:* November 19 through November 25.

Procedure: This patient was tested from November 16 (11 P.M.) to November 19 (5 A.M.). Two pairs of salt-agar-zinc surface electrodes were used; one pair just above the symphysis and one about 2 inches higher. Manual potentiometric determinations of voltage were recorded alternately at five- and fifteen-minute intervals; i.e., a reading was obtained from each circuit every twenty minutes.

Description of Curve: The potentials recorded by the upper pair remained fairly steady throughout the entire experiment. The difference in potentials recorded by the two lower electrodes remained fairly constant during only the first thirty-six hours. At 1 P.M. on November 18 the right lower electrode suddenly became more negative to the left (reference electrode) by 60 mv. The peak was observed at about 2 P.M., the complete rise and fall of the potential occurring within two hours. This was followed by a period of relative steadiness for twelve hours, although the right electrode became slightly positive to the left electrode, as contrasted with its initial slight negativity. Following this there was noted at 2 A.M. on November 19 a second rise of 40 mv. in the same direction as the first increase. It is interesting that, with the single exception of a sudden rise in Miss T. C.'s record (Case 4), we did not obtain this kind of swing in any of the patients who did ovulate during the experiment. The peak occurred here on the twelfth day of the cycle.

Operative Findings: On November 19 (11 A.M.) twenty-one hours after the peak had been attained, laparotomy was performed. The left ovary measured 2 cm. in diameter and contained a follicle which protruded through the ovarian cortex over an area measuring 2 mm. in diameter. The right ovary measured 3 by 2½ by 3 cm. and was filled with many follicles. One of these was about 1 cm. in diameter and had a very thin wall over an area of 4 mm. None of the follicles had been ruptured. Unfortunately the section containing the largest follicle from the right ovary was lost. Prior gross examination, however, indicated its maturity.

The endometrium was in the late proliferative stage.

b. *Duration:* In the first group of four patients (peaked curve), the time required for the attainment of the maximal difference of potential varied from about thirty minutes to eight hours, and the regressions of these potentials showed equally wide ranges.

Within the second group (exemplified by the plateau or inverted U-type curve), the time required for the complete rise and fall of the potentials also varied considerably. The duration of the increase seemed fairly constant (one-half hour to

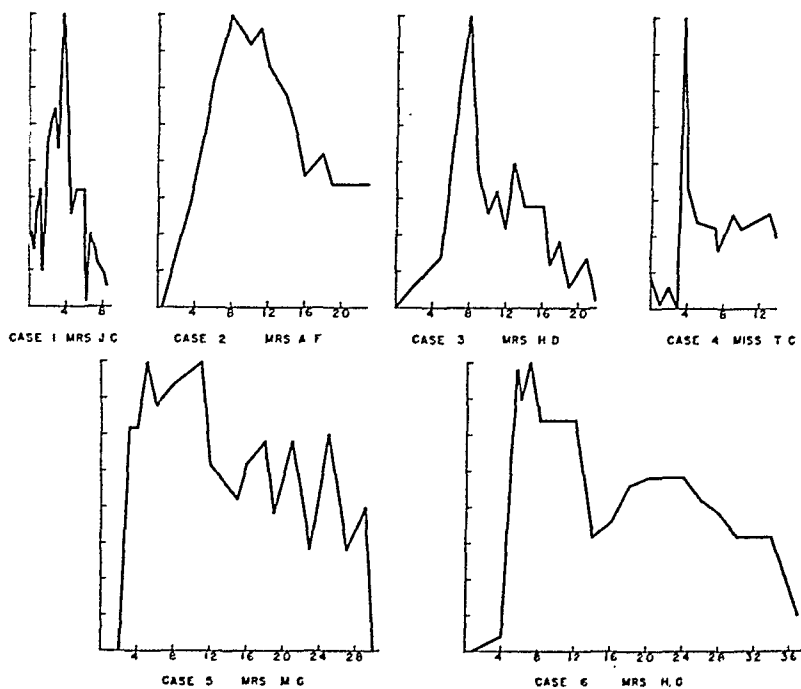


Fig. 1.*—Curves of ovulation potentials.

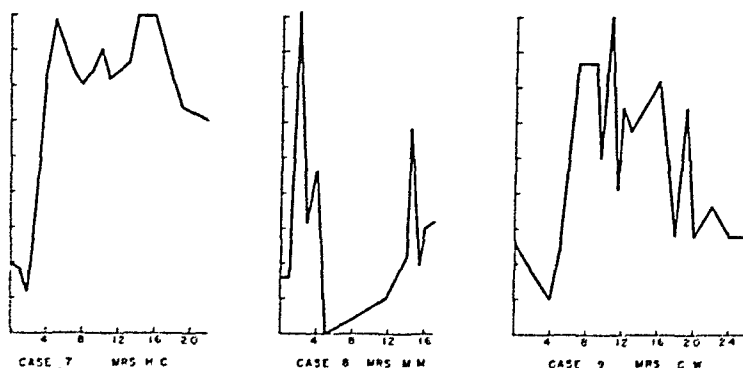


Fig. 2.—Potentials within estimated ovulation time. Mature follicles without rupture.

three hours). The duration of the plateau phase varied from five to twelve hours. The regressions of the potentials also showed wide ranges.

c. *Sign:* In 4 cases where a vaginal-abdominal circuit was employed, with the abdominal serving as reference electrode, the vagina became negative in 3 cases (Cases 5, 7, and 9), and positive in one case (Case 2).

*All curves are plotted as though changes were on the positive side of the reference axis. Figs. 1 and 2 show only the shape of the curve in each case. Each curve has been multiplied by a factor so that the maximum amplitudes are identical. This defines the curve characteristics more clearly. The time relation has been respected. The exact magnitude of potential change is given in the text. Abscissae in all cases are in hours.

CONTROL CASE 3.—Dr. L. E.

This subject was tested from January 3 to January 4. For a period of ten hours the record was flat within ± 5 mv. Then during the next four hours there occurred a very slow rise of potential of about 30 mv. Following this gradual increase there was a decrease to the base line within the space of four hours. This change took place during sleep and was more marked on the lower circuit. The difference of potential between the two upper electrodes remained perfectly steady throughout the experiment.

B. Female Controls.—CONTROL CASE 4.—Mrs. J. S., aged 67 (29 years past the menopause). This patient was connected to the machine on the fourteenth day after a vaginal hysterectomy and perineorrhaphy. Throughout the period February 5 to 9 the record was fairly steady, showing long, slow changes not exceeding ± 10 mv.

CONTROL CASE 5.—Mrs. A. C., aged 47 years.

This patient was tested from April 5 to April 8 (on the sixth to the ninth day after a left trachelorrhaphy). She was connected to the recorder on the seventh day of her menstrual cycle and so was in the nonovulating phase. It may be noted that her endometrium on March 30 was of the late secretory type.

This record does not show any remarkable changes in potential, except for the fact that, whereas during the day the changes were of a magnitude of ± 10 mv., the curve shows a definite flattening at night with changes of less than ± 5 mv. There seemed to be some variation of potential (15 to 20 mv.), associated with mealtimes, appearing on the upper circuit. On two occasions sharp changes (10 to 15 mv.) occurred when the patient voided.

CONTROL CASE 6.—Mrs. M. B., aged 65 years. This patient had passed the menopause twenty years previously. She was tested for four days during recovery from a Fothergill plastic operation performed on April 9. The experiment was started on April 15 and ended on April 19.

For the first two days the record did not show anything remarkable. The remainder of the record had to be discarded because these particular electrodes, due perhaps to drying, offered too high a resistance for the recording device.

EXPERIMENTAL RESULTS

I. *Electrical Changes.*—When the potential differences between two points of the pelvic region, i.e., between the vagina and the abdomen, or between the right side and the left side of the abdomen, were plotted against time, curves of two markedly different shapes were obtained in experiments on nine normal women during their estimated ovulation time.

In four patients (Cases 1, 3, 4, and 8) there was an abrupt increase of the difference of potential from a fairly constant base line (Figs. 1 and 2). The descent from the peak of the curves was fairly prompt and direct; the curves thus resembled an inverted V, which was more or less open, and as a rule rather symmetrical.

In five other patients (Cases 2, 5, 6, 7, and 9) the curves, after a similar abrupt rise, showed a rather extended plateau, and the regression from the maximal difference of potential was less abrupt than was its establishment. Hence these curves more closely resembled an inverted U.

The potentials recorded in these two groups showed wide variations in magnitude, duration, and sign.

a. *Magnitude:* With the exception of one case (Case 1) in which there was some doubt as to the absolute degree of potential increase (page 736), the changes recorded varied from 24 to more than 80 mv.

Study of all the records seems to indicate that the internal circuit has different properties in the various cases, for one gets the impression that when a fairly steady base line is obtained the gross change is usually smaller than when there are large oscillations in the base line.

II. *Correlation of Ovulation with Electrical Changes.*—Of these 9 cases, 5 (Cases 1 to 5 inclusive) were discovered at laparotomy to have ovulated at about the time the potential difference increased. In Case 6 ovulation was placed near this time by the advent of catamenia on the 15th day following the rise in potential. Significantly in the other three women (Cases 7, 8, and 9) the typical potential change was observed, though subsequent laparotomy showed that ovulation, while apparently imminent, had not yet occurred. From one of these patients (Case 7) an ovum which was strongly attractive to spermatozoa was obtained by aspiration of the ripe follicle. Also in Case 9, by aspiration of a follicle which appeared mature on gross examination, an elliptical ovum was recovered. This, perhaps because of faulty in vitro technique, or because of endogenous degenerative changes, did not attract spermatozoa.

DISCUSSION AND CONCLUSIONS

Of prime practical importance are the following questions: What is the time relationship between this observed electrical sign and liberation of the ovum? Does the electrical effect precede rupture? Are the two events synchronous, and is the potential change perhaps caused by the rupture of the follicle? Or does the electrical sign follow rupture?

From our present studies we are led to believe that the electrical change which we have recorded does not follow rupture, nor is it necessarily coincident with it, which we first believed to be the case, and as is true of the change which has been observed in the rabbit. The increase in potential difference may, as in Cases 7, 8, and 9, precede ovulation, and perhaps it always does. That recently ruptured follicles were found in Cases 1, 2, and 4, within twelve hours, and, in Case 5, twenty-four hours after the swing was completed, indicates that if the change in potential precedes the event it does so by only a few hours. When we know more of the development of the corpus luteum, we may judge its age more accurately, and in this way be better able to place the time of ovulation. At the present time it is only possible to characterize this body as (1) *of recent inception*, when the stigma of rupture is still apparent; (2) as *young*, while the coagulum remains and the centripetal capillaries have not yet engrossed all free erythrocytes; and (3) as *mature*, when the luteinized folds appear as solid tissue masses bounded on the periphery by the theca externa, and centrally by a thin layer of modified cells of the theca interna.

Rogers⁹ has shown that in the rat somewhat similar electrical changes are synchronous with exit from estrus. Young and Blandau⁷ emphasize the fact that "in domestic animals as the horse, the cow, the ewe, the sow, and the guinea pig, in which ovulation is spontaneous, it has been found to occur late in the period of heat *or even shortly after its end*" (italics ours). Does this occur in human beings, too, and are these differences in potential caused not solely by the single event of follicle rupture, but rather by a more generalized phenomenon?

It is true that in some of these cases the exceedingly long duration of the process (more than twenty-four hours) seems to point toward a general modification which appears and disappears slowly. There

If we assume that the active ovary was the one containing a ruptured follicle, or a mature follicle, we find, by using surface electrodes, that, out of 4 cases, the active ovary became negative in 2 cases (Cases 3 and 8), and positive in 2 cases (Cases 7 and 4). However in one of these we had evidence that both of the ovaries were fairly active (Case 4) (Table I).

TABLE I. POTENTIAL CHANGE AND FOLLICULAR ACTIVITY

CASE*	POSITION OF ELECTRODES	MAGNITUDE OF BASE LINE OSCILLATIONS MV.	POTENTIAL CHANGE ASSOCIATED WITH FOLLICULAR RUPTURE OR MATURATION MV.	OVARIAN FINDINGS	SIGN OF POTENTIAL CHANGE IN VAGINA OR OVER ACTIVE OVARY
2. Mrs. A. F.	Vaginal-abdominal	± 5	+30	Ruptured follicle in <i>right</i> ovary	Vagina <i>positive</i>
3. Mrs. H. D.	Surface†	± 5	+24	Old corpus luteum in <i>left</i> ovary	Left ovary <i>negative</i>
4. Miss T. C.	Surface	-10 to +16	+80	Young corpus luteum in <i>right</i> ovary, as well as one apparently mature ovum; left ovary contained two apparently mature ova	Right ovary <i>positive</i>
5. Mrs. M. G.	Vaginal-abdominal	± 5	-24	Ruptured follicle in <i>right</i> ovary	Vagina <i>negative</i>
7. Mrs. H. C.	Surface	± 4	-34	Mature unruptured follicle from <i>left</i> ovary. This contained an ovum which vigorously attracted spermatozoa in vitro	Left ovary <i>positive</i>
	Vaginal-abdominal	± 3	-10		Vagina <i>negative</i>
8. Mrs. M. M.	Surface	± 10	-60 -40	Largest follicle in <i>right</i> ovary	Right ovary <i>negative</i>
9. Mrs. C. W.	Vaginal-abdominal	± 5	-25	Large follicle resected from <i>right</i> ovary. This contained an ovum which had recently suffered atresia	Vagina <i>negative</i>

*The first case (Mrs. J. C.) was omitted here because polarity was unfortunately not determined.

†In all cases where surface electrodes were used the left electrode was the reference electrode, so that a change of +24 mv. means that the right electrode was 24 mv. positive to the left.

animals and human beings the external signs of ovulation. The work of Burr, Hill, and Allen on the rabbit has been confirmed and extended to human beings to the extent that the time of rupture of the Graafian follicle may be very closely determined.

Of academic interest in connection with this discovery will be the correlation of the state of the endometrium and the characteristics of the vaginal smears at the time ovulation occurs, and the findings as to the hormone content of the blood and urine in relation to this definite expression of ovarian function. Other metabolic phenomena, such as the temperature and basal metabolism, shown by Rubenstein to reach a low midcycle point may be restudied in connection with this new method. Of scientific interest also will be the assembling of a definite histologic picture of the progressive changes in the ovary in conjunction with the formation of the corpus luteum. From such studies based on the exact time of ovulation may be settled finally the theory of luteinization and the origin of the lutein cells. From Dr. Rock's present finding, I take it, he ascribes the lutein cells to the theca interna. *Similar studies to those of Rogers in the rat may determine the effects upon maturation of the follicle, injections of hormones or other stimulating agents.*

In relation to sterility the determination of the exact time of ovulation is important, in that it will afford an opportunity to determine the optimum time for coitus or artificial insemination or to determine the biological attractiveness of an ovum to the semen of a mate. As far as contraception is concerned, the exact time of ovulation may lead to further advances of our knowledge of the fertile period. Probably further developments and continuance of this mode of investigation will lead to the discovery of other changes of the electrical potentials of the pelvic organs during menstruation or at the onset of labor, or may determine for us the recurrence of ovulation during lactation, and the character of ovulation following hysterectomy. Whether the reaction as expressed by a broad curve is a result of estrus, a general phenomenon, or whether the reaction expressed by a sharp peak is due to ovulation itself alone as a local change seems as yet undetermined.

DR. R. A. ROSS, DURHAM, N. C.—Dr. Rock has mentioned the type of endometrium of one patient, and I would be interested to know whether endometrium was studied routinely and by what procedure? I am also anxious to know if he was able to obtain the ova in each instance. We have employed the technique as described by Newell, Pratt, and Bland with discouraging results.

The description of a corpus luteum given by Dr. Rock is pertinent. Yet we must remember at all times the warning of Hartman as to the unreliability of the appearance of the corpus luteum as an index of its age.

DR. ROCK (closing).—The endometrium was obtained in most of the cases, and in one of them, as I said, it showed the effect of a long progestin influence. The cases in which freshly ruptured follicles were found usually showed the endometrium characteristic of the late proliferative phase. There were no cytologic changes which we could attribute to early progestin influence.

The difficulty of dating the corpus luteum derives from the fact that the luteinization is apparently a progressive process which starts before rupture. At least changes resembling those of luteinization occur in the theca and progress to true luteinization. We have to date our corpus luteum from these changes; i.e., from the thickness of the cell layer, and especially the degree of vascularization. At first there are many open spaces filled with extravasated blood cells which later become lined with endothelium.

We, too, have attempted to recover ova from the tubes but have not been very successful. Once we recovered something which looked like an ovum. I think the difficulty is merely a matter of technique.

I would like to add that we had some controls of these cases. We tested two women who were past the menopause, and another woman during the first week of her cycle, and failed to obtain any curves resembling those which I have shown. Three healthy young males also showed no signs of ovulation.

is, however, no doubt that a local process must occur which is associated with sharply localized potential changes, since we are able to record large differences of potential between 2 nearby points, *a* and *b*, which changes are not recorded between 2 other points, *c* and *d*, no further from the first 2 than are these from each other.

This deduction has been checked by experiments on animals which will be reported later. If a difference of potential is applied across two small silver-silver chloride plates placed anywhere in the peritoneal cavity, the potential changes are recorded with electrodes placed on the skin, and these changes show a strong maximum in the neighborhood of the plates. It seems therefore probable that if, in the experiments reported above, we are dealing with a more general phenomenon (estrus), we are recording its strongly localized (probably ovarian) manifestation. The differences in magnitude, or even in sign, of the potentials recorded would be easy to explain on this basis. On the other hand, the exact relationship between the actual rupture of the follicle and the recorded potential changes constitutes a question which we are at present not in a position to answer with certainty.

Limited as these experiments are in number and duration, they strongly indicate that associated with human ovulation there is a characteristic change in the electrical condition in the pelvis which has not been observed at other times in these cases, or at any time in subjects who have no ripe follicles. So far this change has been identified as an increase of the preceding and succeeding differences in potential between two pelvic electrodes.

It is interesting to observe that a curve suggesting ovulation occurred in all nine cases during the time expected on the basis of current theories of ovulation time.

We wish to acknowledge the valuable assistance rendered by Mr. L. Kingsland (S.B.) in the course of this investigation.

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DISCUSSION

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—The determination of electrical characteristics of the living system has been speeded up by the development of a vacuum potentiometer to measure minute voltage changes in living systems. Through the use of this mechanism it is now possible to determine in experimental

On the eighth day while the ovum is still a free blastocyst the auxiliary cells are already distinctly set apart from the small group of true embryo cells which, having divided but a few times, are still large and retain their primitive unorganized blastomere character. This eighth day marks the completion of what may be regarded as the first and thus the most fundamental stage in the development of the ovum.

There then follows the awakening of the embryo-forming cells which is expressed by proliferation and arrangement of its cells into an ectodermal disc. In the orientation and organization of this embryo or germ-disc it becomes set-off, both dorsally and ventrally by fluid-containing clefts from the abutting auxiliary tissues. The dorsal cleft is first to appear and as it enlarges with the increase of its fluid



Fig. 1.—Implantation of the rhesus embryo as it appears on the thirteenth day. The trophoblastic lacunae are filled with maternal blood and in the immediate neighborhood there is a marked proliferation of the maternal epithelium upon which the trophoblast feeds. Note distention of capillaries. Enlargement 50 diameters. Embryo No. 562.

we recognize it as the amniotic cavity, and its boundary cells are soon fashioned into an amniotic membrane. Similarly, the ventral cleft enlarges to become the combined gut and yolk-sac cavity.

As for the yolk-sac we have seen that it is something more than an embryonic vestige. Furthermore, the yolk-sac does not bud off from the inner cell mass in the form of a solid clump of cells, thereafter acquiring a central cavity, as had been supposed. Nor is it at any time an intrinsic part of, or homogenous with, the gut tract. Instead, the earliest cells of the yolk-sac are differentiated as a thin membrane between which and the gut endoderm there arises the conjoint yolk-sac cavity and gut cavity. This cavity is therefore dual in origin. It

ADVANCES IN OUR KNOWLEDGE OF THE EARLY PRIMATE EMBRYO*

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SUMMARY†

WHEN the three germ-layer theory was perfected by von Baer, it was thought that the fundamental parts concerned in the organization of our body tissues had been found and the ectoderm, mesoderm, and endoderm shown in his beautiful drawings were the three ultimate materials from which our various organs are derived, the three layers being regarded as homogenous in themselves and homologous in all animal forms. This concept seemed to simplify the teaching of embryology and during the subsequent hundred years embryologic and anatomic thought has been dominated by this three-layered topographic analysis, and with a certainty like that formerly prevailing among physicists and chemists regarding the indivisibility of the atom.

As happened with the atom, it is now becoming apparent that the three germ-layer theory in its original diagrammatic form cannot be harmonized with various embryologic observations which have recently been coming from different sources. Improved technique and greater expertness in handling the material have provided us with earlier embryonic stages of the higher mammals including man and monkey, and we can now study under our microscopes beautifully prepared material of a period of development heretofore almost wholly unknown.

We are finding that prior to the laying down of the so-called three germ-layers a more fundamental thing has already taken place, namely, the materials that are to form the envelopes and mechanisms for the attachment and nourishment of the embryo have been separated from the materials that are to form the embryo itself. That is, the developing ovum is composed, on the one hand of "formative substances," to use Hubrecht's term, and on the other hand of "auxiliary substances" which play but a temporary role and are discarded at birth. The segregation of these latter "auxiliary substances" and their precocious differentiation in the form of a trophoblastic shell appear to be the principal results accomplished by the subdivision of the original one-celled egg into a structure consisting of many small cells. This phenomenon of cell-cleavage and the setting apart and precocious differentiation of the auxiliary substances constitutes a fundamental and initial chapter in the development of the embryo.

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†NOTE: This is a brief summary of a more extended paper by the author in a future issue of *Contributions to Embryology*, published by the Carnegie Institute of Washington.

THE INFLUENCE OF LONG-CONTINUED INJECTIONS OF ESTROGEN ON MAMMARY TISSUE*

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A NUMBER of recent experimental studies leave no doubt that *under certain conditions, yet undefined*, sex hormones can awaken a latent impulse capable of inducing malignant changes in a substratum hereditarily susceptible to cancer. The far-reaching importance of such a possibility has led to the issuance of warnings against the empirical use of female sex hormones. While such warnings are timely and well meant, they are prone to create the impression that what strictly applies to animal experimentation applies also to man. However, laboratory findings, until proved applicable, should not be interpreted clinically, but should be viewed strictly in the light of species and strain susceptibilities of the particular animals and tumors studied. In order to clarify the situation, the carcinogenic specificity of sex hormones must be determined and many types of benign and malignant tumors must be studied. This is a difficult task, complicated by a multiplicity of factors. It has been somewhat simplified by the isolation and chemical determination of sex hormones, but there still remains a formidable array of obstacles to be surmounted before the hormone-cancer relationship is better understood.

While a knowledge of the chemistry of the sex hormones is indispensable for an understanding of our problem, we cannot at this time go into a detailed account of their relation to carcinogenic agents.[†] Suffice it to say that the sex hormones belong to the widely distributed group of hydrocarbons of which there are many, ranging from simple anthracene to complicated forms including vitamins, bile acids, sterols, heart poisons, saponins, the morphine group, and the carcinogenic hydrocarbons. It is the relation to this last group that assigns to them a sinister rôle. It is important to know that carcinogenic agents of the hydrocarbon group possess estrogenic properties, just as certain estrogenic substances possess carcinotropic properties. It is of interest that estrogen is chemically related to the sterols, and that the latter may be changed into carcinogenic agents by a process of degradation. The significance of this is evident, since both female and male sex hormones

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†For a detailed account, see L. F. Fieser's *The Chemistry of Natural Products Related to Phenanthrene*, published by Reinhold Publishing Company, New York.

is bordered on its dorsal part by cells that are to form the gut endoderm, an induced product or migratory element from the embryonic ectoderm. Whereas, on its ventral part, it is bordered by the yolk-sac endoderm, which is not an embryonic disk derivative but belongs to the group of auxiliary tissues. The gut and yolk-sac are thus different in origin and are always abruptly demarcated from each other. The one becomes a definite part of the embryo and the other is an auxiliary organ which in primates plays a temporary but probably an essential role in the metabolism of the embryo until the time when its functions are taken over by the placenta, a much more elaborate and efficient organ. Its growth is then arrested, but we can still find its degenerate remnants in the fetal membranes at birth.

Without resort to hypothetical stages or diagrams we have traced the formation of the trophoblastic shell and its implantation. We have seen the setting apart of the amnion and yolk-sac. There remains only the further development of the embryo proper and the formation of its intrinsic organs. It is at this point if you so choose, that the ancient and honorable three germ-layers can be dragged in. But even so I must warn you that they had better be confined to the embryo itself. For any such mechanical analysis is of no help whatever in the understanding of these auxiliary elements of the ovum whose interesting history we have been reviewing.

and transplanted tumors may respond differently to the same biologic condition, although both types furnish equally valuable information in controlled experimentation.

In 1929, when both Doisy and his co-workers and Butenandt isolated estrus-producing hormones in a pure form, they opened up a new field, not only for endocrinology but, for cancer research. Lacassagne, applying this new knowledge, reported in 1932 that male mice ordinarily immune to breast cancer would develop this disease following the prolonged administration of estrogen, although not to the same extent as the females, a very high percentage of which produced mammary cancer under ordinary conditions. Lacassagne, therefore, is the first to link a *particular* sex hormone with a *certain* cancer in mice, demonstrating the correctness of the deductions of earlier investigators. His work, since confirmed by others (Burrows, Bonser, Gardner and others, Cramer and Horning, Loeb and others), has stimulated a very active search for further information on the relationship of endocrines to tumors. Lacassagne, among numerous other observations, has since reported that not all estrogenic substances have the same carcinogenic potentialities for cancer-susceptible mice. For instance, *estrone* possesses more of this quality than *equiline*, and *equiline* more than *equilenine*. He also reported that a combination of *estrone* and hypophyseal extracts would occasionally produce a malignant tumor in mice otherwise refractory to cancer. Lacassagne's conclusions suggest that the carcinogenic potentiality of *estrone* might be part of a biologic mechanism involving the hypophysis. The relation of the hypophysis to tumor growth has been studied by various investigators, and has been discussed by us previously (Emge and Murphy).

Experimental investigations so far cited demonstrate beyond doubt that the female sex gland bears some relation to tumor genesis in a strictly limited field. However, there is as yet no proof that estrogenic substances are carcinogenic agents in an unqualified and general sense. We point this out in order to emphasize that whatever carcinogenic attribute is contained in estrogen must be of a highly specialized nature, capable of acting as a carcinogenic or carcinotropic agent only under certain genetic conditions and, as far as is known, only in tissues directly dependent upon this hormone for functional activities. This is particularly true of breast tissue, which requires estrogen besides other hormones for proper function. Various attempts have been made to determine just how much estrogen is necessary for normal function of the breasts but nothing definite has been learned, although it was observed that the amount of estrogen necessary to stimulate hyperplasia of the breast is generally limited and cannot be pushed beyond a given point (Taylor). This has been confirmed by Howard, who studied proliferative activities of the mammary gland of rats under the influence of acid extracts of pregnancy blood in our laboratory.

The normal estrogen level in living tissues and body fluids apparently is a very variable quantity subject to great fluctuations. Since there is no criterion to serve as a guide, it is not clear to us what is meant by an *excessive* amount of *estrogen* in the blood or tissues. This applies to the statements of Laqueur and others, P. Engel, Dingemanse and others, and Loewe and others, who reported an *excess of estrogen* in the blood of cancer patients and tumor-bearing animals. The same applies to the significance of estrogen levels in tissues. Lewis and Geschickter,

may be obtained from cholesterol. However, only certain chemical components belonging to the estrogenic group so far have shown carcinogenic potentialities and that, only in cancer-susceptible, small laboratory animals (mainly mice). Male sex hormones possess either none or very little of this characteristic, but since they also can be broken down into estrogen by a process of degradation and since sex hormones in general are structurally related to cholesterol, which in turn is related to the most powerful carcinogenic hydrocarbon—methyl-cholanthrene—estrogen as a carcinogenic factor deserves careful consideration.

Until certain endocrine problems were clarified, the study of the hormone-cancer relation was greatly handicapped and consequently slow in developing. In theory, it antedates modern endocrinology by many years, since it really received its inception in 1889 when Schinzinger suggested that mammary cancer might be retarded by the ablation of the ovaries. However, fundamental research of this problem began only in 1907, when Loeb reported that in certain strains of mice practically all males were free from breast cancer, while the incidence was very high in the females. Nine years later, Lathrop and Loeb made an observation which, in the light of Schinzinger's suggestion, is very interesting. They reported that the tumor incidence in mice subject to mammary cancer could be decreased in direct proportion to the time of castration, and this has been confirmed by Murphy and Sturm, and Cori. Lathrop and Loeb found that *early* castration would markedly reduce the cancer incidence in the females, and in fact would almost nullify it. These experiments emphasized the importance of the age factor, for if castration were postponed until the eighth or tenth month of life malignant growth could be retarded but slightly. An attempt to offset the influence of castration by the grafting of ovaries from related animals failed (Loeb, Cori). However, Murray demonstrated in 1928 that this could be achieved by using ovaries from sisters. He blamed previous failures to strain differences not sufficiently eliminated by inbreeding. In his experiments, cancer-resistant males were implanted after castration with sister ovaries, resulting in 7.1 per cent of cancer in these otherwise cancer-immune males. Murray also demonstrated that in the strain of mice used by him *virginity* markedly decreased the tumor incidence. His castration experiments verified the conclusions of Loeb and Cori.

In our experience with more than 5,000 transplantable mammary tumors of the white rat we have observed a variety of responses to castration. For instance, certain fibromas and adenofibromas would not grow before sex maturity unless the animals had been castrated or continuously injected with estrogen. While this conforms with the results of others, the character of the tumor must be taken into consideration. We found that certain mammary sarcomas were not influenced by the age of the host, since they could be transplanted into young or old rats with equal ease regardless of castration. Recently Sauerbruch and Knake also reported an increase in cancer susceptibility in rats after castration. It must be considered, however, that spontaneous

duced by prolonged injection of corpus luteum extracts (Nelson and Piffner) is to be expected, and adds nothing to the knowledge of the relation of tumor production to sex hormones. Witherspoon's deduction that uterine fibroids are due to hyperestrinism resulting from cystic ovaries is also interesting, but cystic ovaries do not necessarily accompany fibroids. His report that endometrial hyperplasia was the precursor of fibroid tumors in 44 patients observed for a number of years is of more importance. It is generally assumed that endometrial hyperplasia is related to hyperestrinism, and since fibroids ordinarily shrink after the menopause, it is logical to link these tumors with some form of estrogenic imbalance. The mechanism probably is not as simple as that, because if fibroids and mammary cancer result from prolonged hypersecretion of estrogenic substances, why does not breast cancer occur oftener in women growing fibroid tumors of the uterus?

As far as the carcinogenic factor in estrogen is concerned, no more can be said at present than that estrogen increases the incidence of mammary cancer in certain strains of susceptible mice and occasionally in rats (Gardner and others, Burrows, Bonser, Cramer and others, Suntzeff and others), and that in these animals it can incite cancerlike tissue proliferation of the cervix and vagina (Engle and Smith, Suntzeff and others) but only occasionally produces a true cancer (Gardner and others). None of these observations prove that estrogen is the sole factor involved, and as far as small animals are concerned, one may even go so far as to state that it is possible that estrogen becomes a carcinogenic factor only when a hereditarily prepared substratum for cancer exists. Nothing is known of the effects of prolonged administration of estrogenic hormones in human beings. Mazer and Israel recently reported a fairly large series, and there is nothing in their report to indicate that tumor growth was stimulated. However, since Loeb pointed out that the effect of hormones on tumor production in experimental animals may be delayed, it is very worth while keeping an eye open for untoward effects in clinical medicine, particularly in relation to breast reactions. So far, we have never seen an aggravation of cystic disturbances of the breast during treatment with estrogenic or chorionic hormones. In fact, these hormones commonly relieve the discomfort of the patient and cysts frequently diminish in size. However, the effect of any female sex or chorionic hormone on cystic breasts is variable and unpredictable. Some breasts will not respond to one but to another, or vice versa, and therefore we doubt that the action of either is specific and direct.

Apparently the endocrine control of the mammary gland is equally as complicated as that of other secretory organs depending upon cyclic hormonal impulses. It is certain that the growth of this gland is dependent upon the ovary and probably responds to its stimulation in a direct ratio to the normal estrogen-progestin interchange. If estrus is prolonged, ducts may proliferate, as observed in the rabbit by Ancel and Bouin. However, in animals with short estrual phases such as occur in the rat, the cyclic response in breast tissue may be negligible. If the luteal phase is prolonged, as happens with sterile copulation, the mammary gland may show proliferative activities similar to those observed in the first half of pregnancy. Evans and Simpson noticed that after

and Heiman and Krehbiel reported the presence of excessive amounts of estrogen in pathologic breast tissue of women and tumor-bearing rats, but neither Frank and his co-workers nor Mohs could confirm this. Frank, Goldberger, Salmon, and Friedman found that normal muscle tissue could store estrogen without showing unusual growth activity, and Mohs reported that the estrogen content of mammary adenofibromas of the rat was very low and could not be increased by the continued injection of estrogen. He expressed doubt that the growth ability of the mammary adenofibroma used by him was dependent upon a concentration of estrogen in the tumor tissue, and Frank and his co-workers warned against making general conclusions on the sole basis of finding estrogenic substances in abnormal tissue because this may be only a normal occurrence similar to that of glycogen storage in muscle, which is increased or decreased as conditions demand.

A number of attempts have been made to extend the principle of Lacassagne's experiments to other tissues and animals. McEuen showed that estrogen, like other carcinogenic agents, could produce endometrial hyperplasia, but not malignancy, in rats. Overholser and Allen, and Hisaw and Lendrum observed, after prolonged estrogen administration, the formation of lesions on the monkey's cervix which resembled very early malignancy, but since these lesions disappeared after estrogen was discontinued, or was neutralized by corporin (corp. lut.), it is safe to assume that cancer was not actually produced.

Several investigators have attempted to create a favorable state for hyperplasia to be acted upon by estrogen by resorting to mechanical or biochemical traumatization. Overholser and Allen did so with the monkey's cervix, with the result reported. Burrows combined tarring and estrogen administration and reported that the resulting tissue proliferation and metaplasia *rarely* reached a cancerous state if the animals were refractory to tarring. Perry and Gintzon applied a combination of 1:2:5:6 dibenzanthracene and estrogen to the skin of mice, which was followed by the appearance of numerous benign and some malignant tumors. These are interesting experiments but the introduction of several factors unfortunately beclouds the issue and therefore sheds no light on the specificity of estrogen as a carcinogenic agent.

In 1934 Engle and Smith, and more recently Suntzeff, Burns, Moskop, and Loeb, reported that prolonged administration of estrogen to susceptible mice leads to proliferative changes in the cervix and vagina which are not unlike carcinomatous degeneration. These very extensive and thorough studies led the authors to conclude that the changes observed are not compatible with the view that somatic mutations in the stimulated tissues are the immediate cause of their cancerous transformation. In confirmation Gardner, Allen, Smith, and Strong described the appearance of tumors in or near the cervix of cancer-susceptible mice after prolonged administration of large doses of estradiol benzoate. Since one of these tumors proved to be a transplantable carcinoma, the significance of this finding is evident. MacDonald, as well as Howard, attempted to produce unusual cell proliferation in the breasts of rats and rabbits by prolonged administration of estrogen, progestin, pituitary extracts, and pregnancy blood, but reported that no malignant changes resulted. Bischoff and Maxwell failed to influence the behavior of transplantable mouse sarcoma and mammary carcinoma by similar methods. That deciduomas can be pro-

The results recorded in Table I suggest that estrogen bears a relation to implantability and growth of tumor implants. However, growth variations in the estrogen groups are too wide and the series too small to permit final conclusions.

TABLE I. PERIOD OF TREATMENT: 210 DAYS

	NORMAL CONTROL MALE AND FEMALE	CASTRATES MALES	THEELIN TREATED MALES	CASTRATE FEMALES	THEELIN TREATED FEMALES
Age: 40 days					
22 animals	5	6	3	5	3
Per cent takes	0	83	100	20	66
Daily tumor gain	0	+0.19	+0.03	+0.36	+0.21
Daily body weight change	+0.47	+0.45	+0.44	+0.44	+0.47
Int. units theelin			10,500		10,500

	CON- TROL MALES	CASTRATE MALES	THEELIN TREATED MALES	CONTROL FEMALES	CASTRATE FEMALES	THEELIN TREATED FEMALES
Age: 90 days						
23 animals	3	6	3	2	6	3
Per cent takes	100	50	33	100	83	100
Daily tumor gain	+0.44	+0.09	+0.02	+0.76	+0.10	+0.05
Daily body weight change	+0.12	+0.44	+0.31	+0.03	+0.37	+0.26
Int. units theelin			10,500			10,500
Daily injections: 50 I.U.						

Being occupied with other investigations related to the growth problems of these tumors, we did not undertake further estrogen studies until 1936, when we studied the relation of varying amounts of theelin given over long periods of time to animals implanted with a mammary adenofibroma of great growth potentialities (Emge, Murphy, and Schilling). This tumor has been transplanted by us for eight years and has maintained its adaptability to hormonal stimulation. As is readily seen from Figs. 1 and 2, it responds vigorously to the stimulation of pregnancy. However, when it is implanted into males, it tends to lose its alveoli, forms ducts, or transforms itself into a connective tissue tumor. By continuing transplantation it can ultimately change into a vicious sarcoma. We therefore wondered if hormones had any part in this process. We were particularly interested in finding whether an estrogenic hormone could arrest the change from adenofibroma to fibroma, and since none of our adenofibromas has ever produced a carcinoma in the ordinary course of transplantation we were interested also in learning whether estrogen could induce such a malignant change.

As previously reported (Emge and Murphy), we learned that rapidly repeated pregnancies create a marked hyperplasia in these tumors. We used this method in the hope of producing uncontrolled hyperplasia but came to the conclusion that neither the massive hormonal stimulation of pregnancy nor the long-continued storage of secretion would create an unusual hyperplasia, and that pregnancy was not a factor in producing or hastening the development of sarcomas. We found that the

injecting anterior pituitary extracts containing a luteinizing factor, rats' breasts would show a thickening of gland and lactating phenomena corresponding to changes seen in the latter half of pregnancy.

It is of further interest that the mammary gland of the male rat is usually limited to the development of ducts. We have found that implanting mammary adenomas from females into males leads to a disappearance of alveoli in many instances. Male rats show an insignificant estrogen level, although Turner demonstrated readily detectable amounts in the feces of certain males. Since the male has a paucity of estrogen and presumably a mammary gland free from cyclic changes, it occurred to us that the implantation into these animals of adenofibromas capable of certain mutations offered an excellent opportunity to study the effect of prolonged administration of estrogen* upon both the tumor and the host. We fully realize that the injection of hormonal substances may set up a trend of events quite different from normal occurrences, but since neoplastic tissue changes are not normal, this form of experimentation is at least not illogical. We are aware that chemically prepared endocrine substances may differ, and we are investigating this factor at present.

We have been studying the growth behavior of transplantable mammary tumors of the rat since 1929. As previously reported (Emge), our tumors have shown a remarkable ability to undergo mutations ranging from various types of adenofibromas to those of fibromas and fibrosarcomas. The mechanism underlying the changes occurring in the course of transplantation has puzzled us greatly, and in an attempt to unravel the complicated process, we have at various times resorted to experimentation along the lines of a hormone-tumor relationship. Our attention was first called to this when we surveyed the transplantability of certain of these tumors in 400 male and female white rats of the Wistar strain, and we found that successful transplantation was in direct proportion to age. Rats under sixty days of age, regardless of sex, rarely grew tumors. From the age of sex maturity (about 90 days) to 250 days, the percentage of successful "takes" reached its maximum, and decreased when the animal passed into the third trimester of its natural life. Old animals, also, were difficult to implant, but on further investigation we found this to be true only of benign tumors. Sarcomas derived from the latter were no respecters of age and could be grown at any age. Following this survey, we undertook a short study (1932), not published, in the hope of obtaining further information on the age factor in relation to the transplantation of benign mammary tumors. We implanted 45 animals 40 and 90 days old, some of which were castrated, with the same mammary tumor. After implantation, 50 units of theelin were injected daily under the skin of a certain number of castrates for 210 days. Control rats 40 days old failed to grow tumors, but those 90 days old did so in every instance.

*All experiments reported here were done with *aqueous* theelin (Ketoxyhydroxyestrin), generously donated by Parke, Davis and Company through the courtesy of Dr. E. A. Sharp.

have here a mammary adenofibroma incapable of abnormal estrogen storage, possessing sarcomatous tendencies, but lacking the ability to produce carcinoma. We were then interested in determining what effect various dosages of estrogen administered over varying periods of time would have on this tumor when grown in males and females of

Fig. 5.

Fig. 6.

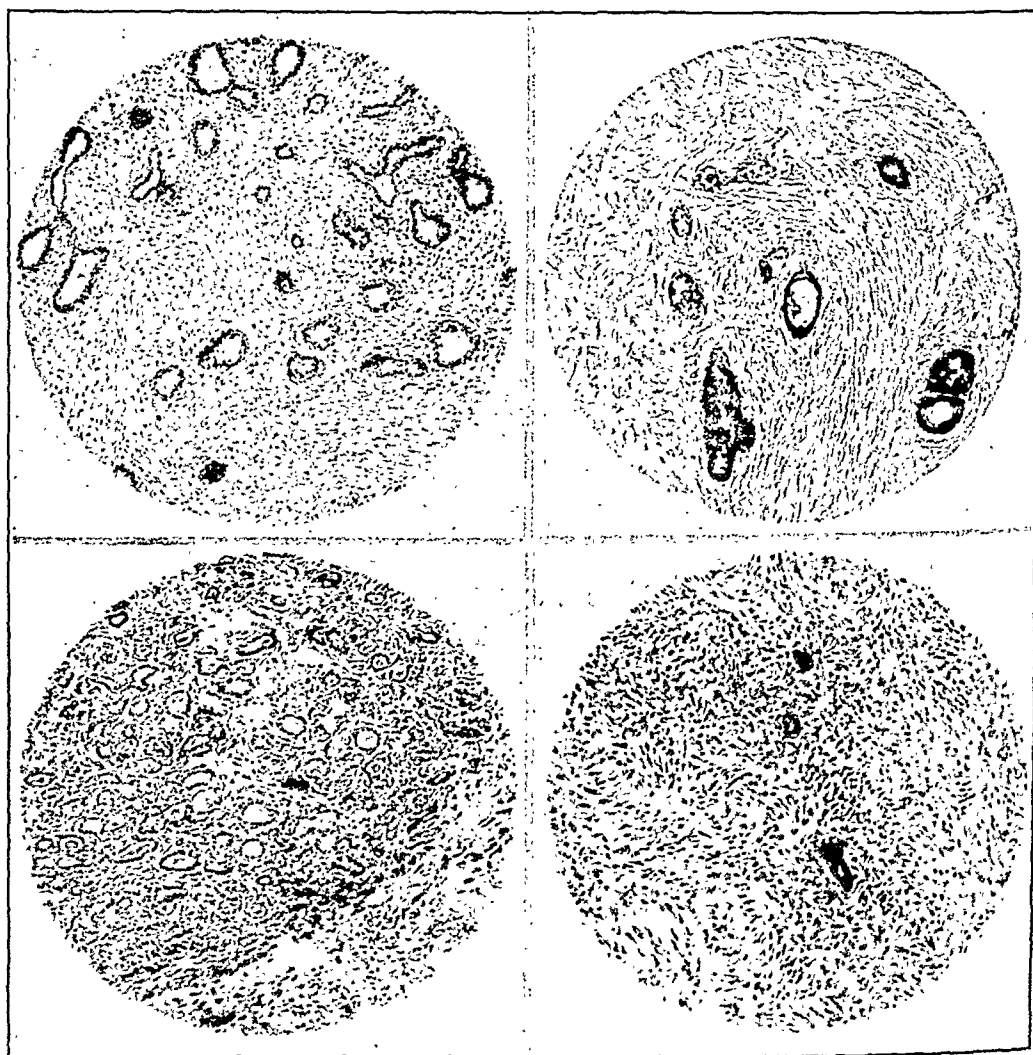


Fig. 7.

Fig. 8.

Fig. 5.—Female donor to Experiment 2. Diffuse adenofibroma.

Fig. 6.—100 I. U. theelin treated male of Experiment 2. Fibroadenoma showing reduction of glandular material. Demonstration of slight ductile proliferation. Stroma fibromatous, without unusual activity.

Fig. 7.—Female donor to Experiment 3. Adenofibroma with abundant glandular material. Secretion present. Five pregnancies during tumor growth span. Tumor removed five days postpartum.

Fig. 8.—Male control of third experiment. Adenofibroma showing a loss of glandular elements upon transplantation into males. Predominantly a pure fibroma with occasional small gland.

different ages. The particular rats used in this study are derivatives of the Wistar strain, in our possession since 1903, heavily inbred, and as far as we know, entirely free from spontaneous malignancies.

massive hyperplasia, which subsided during puerperal involution, was entirely dependent upon the maintenance of the pregnant state (Figs. 3 and 4).

We next undertook a study of the estrogen content of various adenofibromas and their derivatives and found exactly as Mohs reported that neither adenofibromas nor sarcomas possessed an unusual estrogen con-

Fig. 1.

Fig. 2.

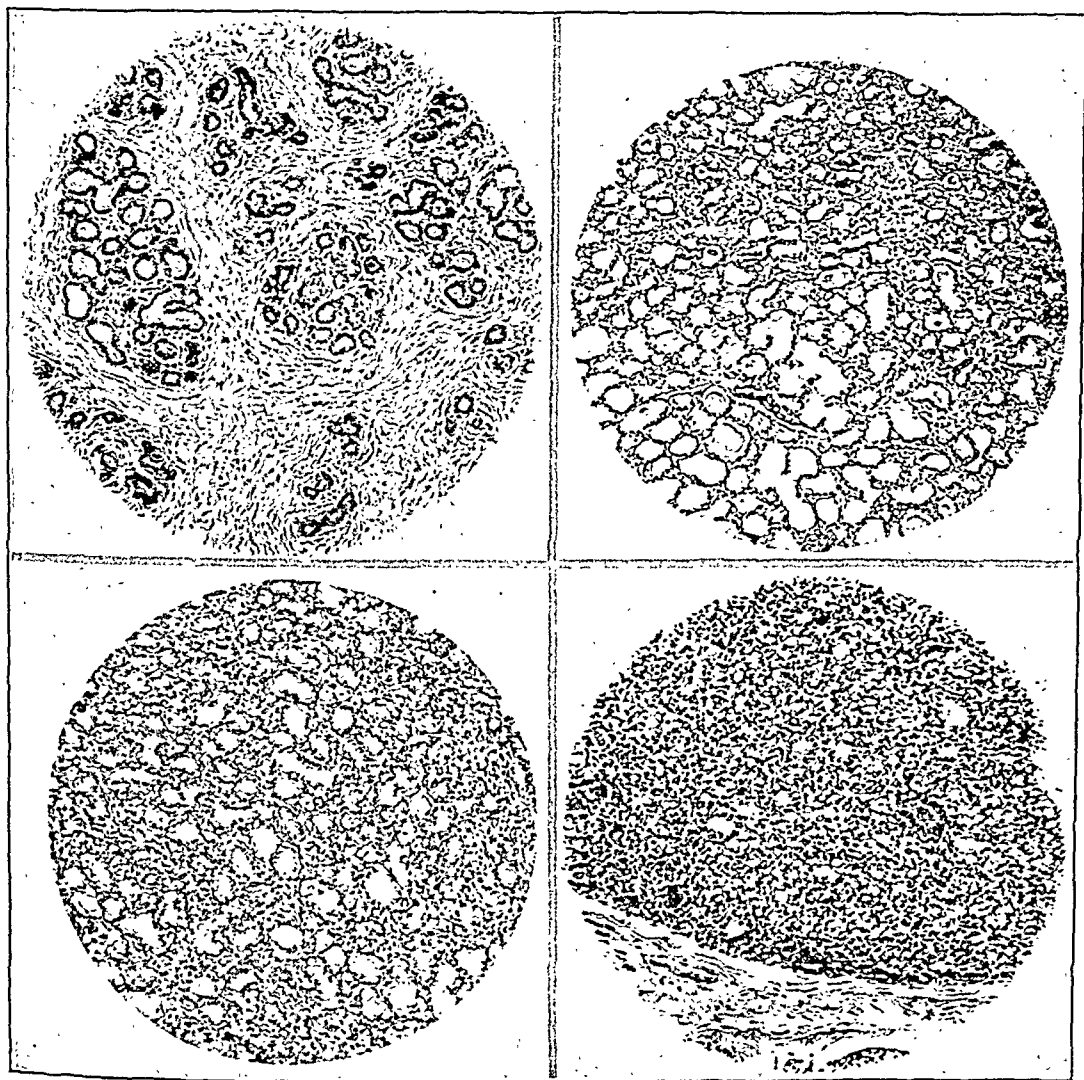


Fig. 3.

Fig. 4.

Fig. 1.—Control. Adenofibroma showing usual whorl type with a compact stroma.

Fig. 2.—Female seven days postpartum. Adenofibroma demonstrating lactation reaction of pregnancy.

Fig. 3.—Two pregnancies. Tumor removed at term. Adenofibroma showing massive hyperplasia of gland tissue and abundance of secretion.

Fig. 4.—Three pregnancies during tumor growth period. Tumor removed sixteen days postpartum. Adenofibroma with hyperplastic glandular epithelium. Basement membrane broken in some areas. Secretion and mast cells present.

tent. Dr. C. F. Fluhmann, who investigated the estrogen levels of these tumors for us, reported that prolonged administration of this hormone did not raise the estrogen level beyond that expected. We therefore

This was not so of the younger group, and the significance of this is not clear to us. In all of the injected animals, there occurred a marked decrease in the weight of the liver and a reduction in body weight, quite similar to that of the previous experiments. The tendency of the tumor to develop into a cellular fibroma and the general behavior of the glandular tissue toward duct formation at the expense of the alveoli were also observed in this series (Figs. 8 and 9). However, there was one 160-day-old injected male which developed a tumor of unusual hyperplastic tendencies. Essentially this affected the ducts but, as can be seen in Figs. 10 and 11, alveoli were also involved. There was a marked increase in the layers of cells in the alveoli with a tendency to papillomatous degeneration. The marked distention of the ducts by secretion is evident. There can be no doubt that this tumor developed greater unusual activities than previously observed in many hundreds of transplantations. Tissue from this tumor was autoimplanted into the same host and the injection of theelin continued for thirty-seven days, when

TABLE III. PERIOD OF TREATMENT: 163-368 DAYS

	AGE: 160 DAYS (ALL MALES)		AGE: 300 DAYS (ALL MALES)	
	CONTROLS	THEELIN TREATED	CONTROLS	THEELIN TREATED
39 animals	8	12	7	12
Per cent takes	63	50	43	42
Daily tumor gain	+0.06	+0.02	+0.02	+0.05
Daily body weight change	+0.30	+0.20	+0.15	-0.09
Total Int. units theelin		2,300-5,200		2,300-5,200
Autopsy weights of:				
Testes	2.45	2.45	2.06	1.55
Pituitary	0.015	0.014	0.014	0.013
Adrenals	0.073	0.050	0.055	0.172
Thyroid	0.059	0.052	0.044	0.045
Spleen	1.28	1.14	1.12	1.21
Liver	19.29	15.06	16.00	12.81
Kidneys	3.08	2.75	2.99	3.08
Bi-weekly injections: 50 I.U.				

the animal unexpectedly died. The study of the autoimplantation revealed that the glandular component of the tumor had become predominant over the connective tissue element, orderly arrangement of glandular structures disappeared, and the tumor was permeated with long strands and masses of cells of irregular size, highly suggestive of a malignant state (Fig. 12). However, the normal mammary tissue of the host did not show any of these changes. In fact, none of the normal mammary tissue of any of the injected animals showed a greater response to theelin than would be expected from prolonged administration of the hormone. Ducts and tubules showed a fair amount of cellular activity but in only two animals was the proliferation sufficient to approach the Schimmelbusch type. Alveoli showed some abortive attempts at the formation of lobules. Fibrosis was not significantly increased. It therefore can be stated that the injection of theelin in the amounts

In designing our experiments we took into consideration the fact that a transplantable tumor may act differently from tissue growing in situ. In order to obtain information about such differences we not only studied the behavior of the transplanted mammary tumor but that of the normal mammary breast tissue as well. In the second experiment, 32 animals implanted with a diffuse adenofibroma* (Fig. 5) were divided into three groups, the first serving as controls, the second receiving 100 I.U., and the third 200 I.U. of theelin daily for 77 days. The tumors grew as indicated in Table II, with the usual variations in size, but no unusual growth behavior attributable to the injection of the estrogenic hormone could be demonstrated grossly. The animals receiving theelin showed a slight, but definite, loss in body weight (Emge, Murphy, and Schilling). In spite of the long-continued injections of estrogen, the tumors tended toward fibromas with a definite reduction of adenomatous material. Ducts showed a slight but unusual tendency to proliferate, and connective tissue elements showed no greater cellular activity than in routine transplantation (Fig. 6). In other words, the estrogenic

TABLE II. PERIOD OF TREATMENT: 77 DAYS

	CONTROL MALES	THEELIN TREATED MALES (100 I.U.)	THEELIN TREATED MALES (200 I.U.)	CONTROL FEMALES	THEELIN TREATED FEMALES (100 I.U.)	THEELIN TREATED FEMALES (200 I.U.)
Age: 140 days						
32 animals	5	6	6	5	5	5
Per cent takes	60	60	83	60	50	60
Daily tumor gain	+0.04	+0.05	+0.02	+0.46	+0.06	+0.11
Daily body weight change	+0.32	+0.13	-0.05	+0.25	+0.18	+0.17
Total Int. units theelin		8,000	16,000		8,000	16,000
Autopsy weights of:						
Testes	2.57	2.54	2.64			
Ovaries				0.076	0.086	0.084
Pituitary	0.012	0.010	0.010	0.010	0.011	0.012
Adrenals	0.048	0.031	0.025	0.066	0.042	0.050
Thyroid	0.055	0.052	0.048	0.040	0.037	0.040
Spleen	1.23	1.22	1.63	1.59	1.36	1.26
Liver	10.68	12.45	10.55	10.44	10.25	9.29
Kidneys	1.81	1.83	1.82	1.58	1.45	1.42
Daily injections: 100 or 200 I.U.						

hormone did not arrest the reduction of glandular tissue nor produce unusual hyperplasia, nor did it stimulate connective tissue to unusual activity.

Acting on Loeb's suggestion that the prolonged use of estrogen might prove more important than the dosage, a further experiment was done, in which 39 animals 160 and 300 days old were given 50 I.U. of theelin bi-weekly over a period of 163 to 368 days (see Table III). The tumor used for implantation showed abundant glandular material (Fig. 7). Neither age group showed any significant differences in the number of "takes," tumor growth rate, or daily tumor gain. The testes of the older animals weighed less and the adrenals more than the controls.

Autoimplants made in 15 animals of this experiment and treated with the same amount of theelin failed to yield further information. The tumors, instead of tending toward the cellular types, produced marked hyalinization. Seven animals which previously had failed to grow tumors were implanted with another rapidly growing adenofibroma, which also failed to grow. These animals, as well as the autoimplanted group, were given 50 units of theelin bi-weekly for 70 days, the total period of treatment covering 233 to 438 days, or nearly half the life span of a rat.

Being curious as to what would happen to tumor tissue from a theelin-treated male if transplanted into females and the theelin injections continued, we implanted tissue from a rapidly growing fibroma giving in-

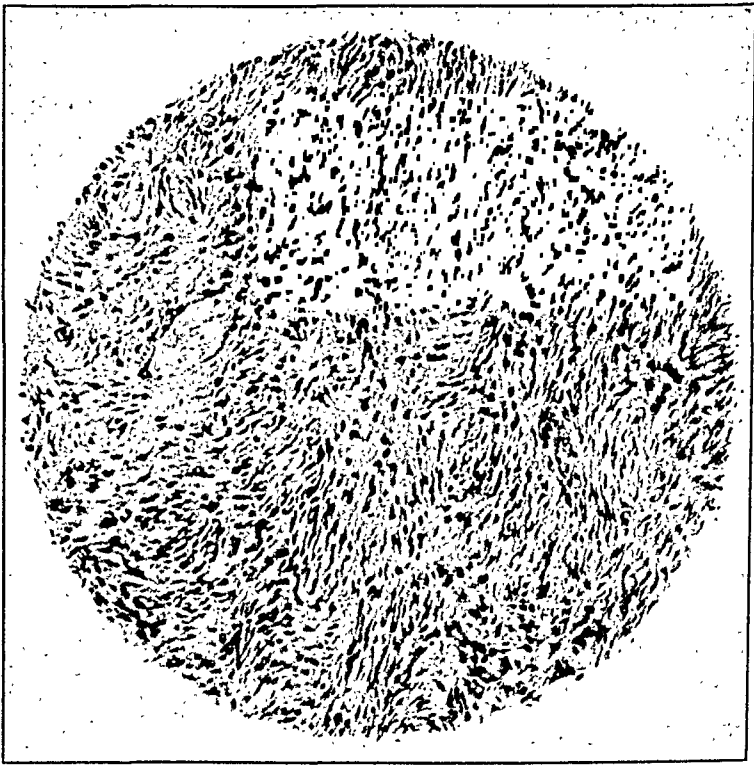


Fig. 13.—Theelin treated male of Experiment 3. Donor to Experiment 4. Very cellular fibroma with indications of sarcomatous tendencies.

dication of sarcomatous tendencies from Experiment 3 into 24 females and 12 males (Fig. 13). Twelve of the females were used as controls. The remainder were treated bi-weekly with 50 I.U. of theelin for 20 weeks. This tissue grew in about 75 per cent of all animals, and there was no essential difference between controls and injected animals (see Table IV). The implanted tumor was of a very cellular type, such as frequently preceded sarcomatous degeneration in subsequent transplantations. However, it contained many mast cells, and we are under the impression that when these cells are present sarcomatous degeneration will not develop readily. No unusual growth behavior was noticed. The growth rate was ordinary, and there were no further connective

indicated did not create any unpredictable changes in the normal mammary tissue of male rats of our strain.*

We concluded that while estrogen ordinarily did not influence the behavior of this mammary tumor any differently than in the previous experiment, the occurrence of an unusual hyperplasia with malignant tendencies in a tumor implanted in a younger animal might be of sig-

Fig. 9.

Fig. 10.

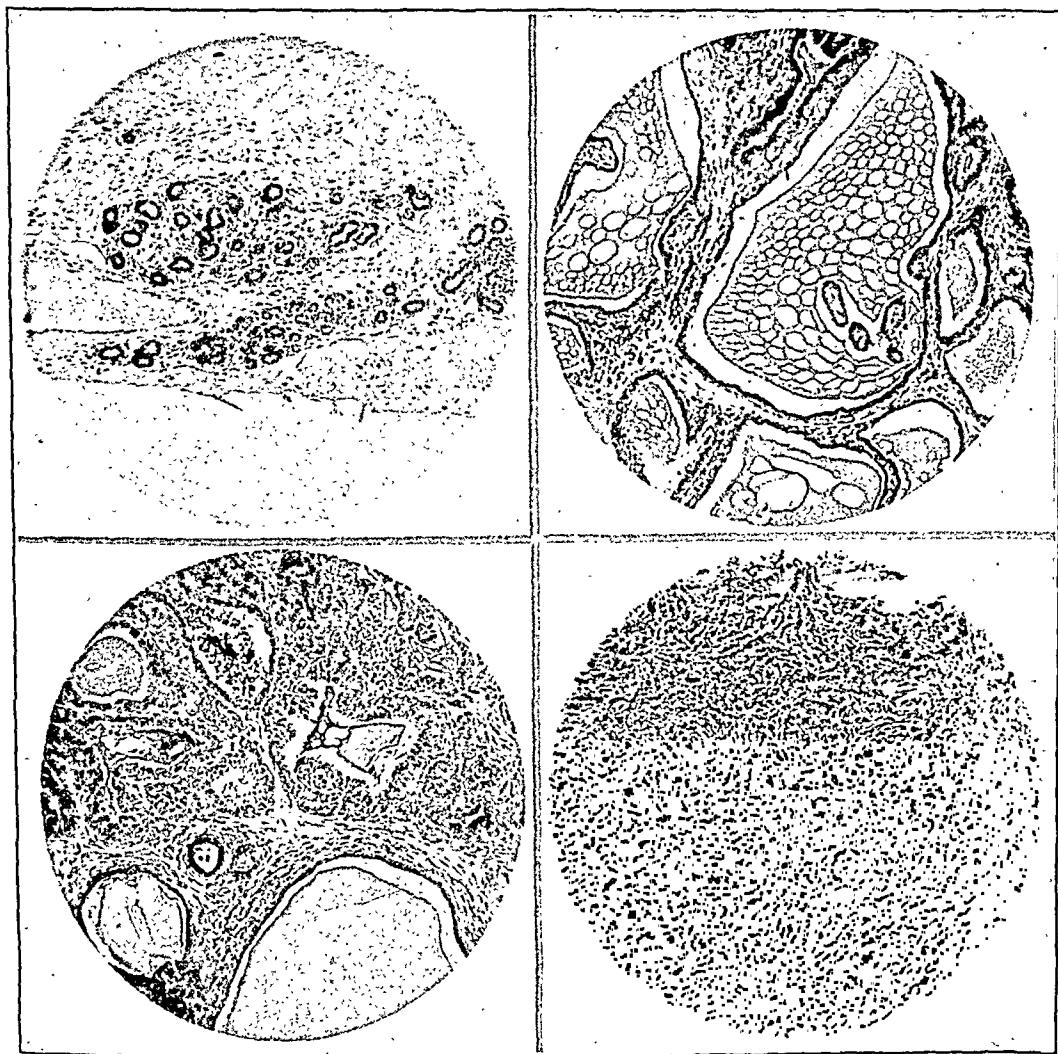


Fig. 11.

Fig. 12.

Fig. 9.—Male control of third experiment. Adenofibroma with groups of small glands without secretion.

Fig. 10.—160-day theelin treated male of Experiment 3. Adenofibroma showing unusual hyperplastic tendencies, densely packed with ducts and glands. Demonstration of tremendous ductile proliferation.

Fig. 11.—Another area of tumor of Fig. 10, showing massive areas of alveoli proliferation with considerable secretion.

Fig. 12.—Autoimplantation of tumor of Figs. 10 and 11. Demonstration of predominance of glandular components and loss of organization, suggestive of a carcinoid state.

nificance. We are now repeating this experiment with a larger group of animals and with larger doses of the hormone, using the oily solution instead of the aqueous substance.

*A detailed cytologic study of the mammary tissue will be reported elsewhere by Dr. N. J. Howard.

tumor developed a carcinoid tendency. Therefore, a susceptible substratum existed only in *this* tumor, while neither the tumor mates nor the normal mammary glands of the tumor hosts showed signs of this characteristic. We expect it to be said that the dosage used by us was insufficient and that an aqueous preparation might act differently from an oily preparation. Granting the merit of this objection, we still consider the dosage not only adequate but excessive for the size of the animal used in these experiments, since it depressed the normal body weight gain. It is our opinion that the employment of larger doses would produce results not comparable with ordinary biologic occurrences. The important information sought is the response of functionally susceptible organs to long-continued administration of sex hormones in doses comparable with those used in clinical medicine. This, to us, is far more significant than the happenings following immense doses of sex hormones used in experimental studies.

Although we believe that the carcinogenic importance of estrogen is strictly limited by biologic conditions to certain tissues in certain species of mammalia, we feel that this evidence is still not sufficient to warrant the abandonment of caution in the use of large doses of this hormone in clinical practice. We have no knowledge of the latent effects of estrogenic hormones in higher mammalia, and until we do, vigilance is in order.

CONCLUSIONS

1. Transplantable mammary adenofibromas known to possess malignant potentialities were refractory to the influence of estrogen with the exception of one tumor, in which a carcinoid state occurred.

2. Estrogen did not prevent the loss of glandular tissue in mammary adenofibromas known to do so in the process of continued transplantation.

3. Tumors known to undergo sarcomatous changes did not show an increased sarcomatous tendency when exposed to continued estrogen administration.

4. Various dosages of estrogen administered to rats of different ages over long periods of time did not produce breast tissue changes beyond those expected for long estrogen stimulation.

The technical services of Mr. Pierre Lassagues and Mr. L. M. R. Wulff are gratefully acknowledged.

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TABLE IV. PERIOD OF TREATMENT: 139 DAYS

	CONTROL FEMALES	THEELIN TREATED FEMALES	THEELIN TREATED MALES
Age: 143-190 days			
36 animals	12	12	12
Per cent takes	83	58	75
Daily tumor gain	+0.12	+0.05	+0.13
Daily body weight change	+0.24	+0.23	+0.45
Total amount theelin		2,000 I.U.	2,000 I.U.
Bi-weekly injections: 50 I.U.			

tissue changes suggestive of sarcomatous degeneration. This tumor, although showing cytologic changes of the sarcomatoid type when exposed to long-continued injections of estrogen, did not degenerate into sarcoma.

DISCUSSION

The carcinogenic potentiality of the sex hormones is apparently extremely variable. Estrogen appears to possess this particular quality to a greater degree than other sex hormones. However, this quality seems to be strictly limited by certain biologic circumstances. There can be no doubt that estrogen plays some rôle in the production of a cancerous state of mammary, and occasionally of uterine, tissue of *mice susceptible to cancer*. It is equally important that little or none of this quality is shown in mice refractory to cancer, and it is further important that other rodents, particularly the rat, show far less susceptibility to this hormone than mice; and larger animals, as far as is known, remain entirely unaffected. We may therefore correctly assume that the carcinogenic potentialities of estrogen are limited by species differentials and probably by organ differentials and individuality characteristics. It seems likely that only tissues hereditarily prepared for unlimited hyperplasia can respond to the estrogenic impulse, and then, only under certain definite conditions. The mechanism of the hereditary transmission of this factor is still in dispute. Slye assumes that it follows the Mendelian rule, while Little considers it an extrachromosomal process. Whatever this mechanism may be, it is subject to the action of another factor yet unknown, which permits estrogen to change unlimited hyperplasia into uncontrolled tissue growth, or cancer. Probably the rôle played by estrogen is somewhat of the nature of that played by the nematode in Fiebigger's experiments, which prove that carcinoma of the stomach of the rat can be produced only if the right kind of nematode is fed to a particular cockroach, in turn fed to a particular kind of rat. If any of the factors were disturbed no carcinoma developed, and with all factors equal, carcinoma could be produced *only* in the stomach.

In our own experiments, some of this is illustrated. Both the transplanted and the normal mammary tissue are known to possess the ability for hyperplasia and a capacity for malignant degeneration of connective tissue structures. Although both tissues responded well to hormonal stimulation, their behavior was not influenced by the amount of estrogen administered or the length of treatment except in one instance, when a

Lacassagne, one of the leading workers in this field, has been able to produce adenocarcinoma of the mammary gland in the male mouse by prolonged injections of estrone. Following the course of treatment, the growth appeared in 100 per cent of animals, both male and female, between the third and tenth months, the growths developing in a strain of mice in which one might expect tumors in only 72 per cent, only in the female and at the average of one year. Thus it is shown that if an artificial development of the male breast equal to that of the female is produced, the incidence of carcinoma of this organ will be the same in both sexes. He states that this finding does not prove whether the important cause for the development of the cancer is an hereditary factor or if it is solely the stimulative action of the hormone. In order to solve this problem he used a strain of mice in which only 2 per cent of the females spontaneously developed mammary carcinoma, the estrone injections in the male being given weekly from shortly after the time of birth. After eight months, none of the surviving animals developed growths, while in a similar period almost all of the mice of the strain previously studied died of adenocarcinoma of the breast. However, beginning with the ninth month, malignant tumors of the breast appeared, until between the twelfth and eighteenth months all the mice of this strain died of malignant growths of the breast. Here is demonstrated the fact that carcinoma will develop in mice of low cancer strain but will be greatly retarded in its development. In a final incomplected experiment he injected estrone, under the same conditions, into mice in which spontaneous cancer of the breast had never been observed. In twenty of these animals which survived more than six months, neither male nor female developed a breast tumor. The results of these three experiments show that the two most important influences in the production of mammary adenocarcinoma in the mouse are the hereditary and the hormonal factors.

Even with the great accumulation of experimental data at hand, obtained mainly from work on the mouse, we have to my knowledge very little positive information as to the carcinogenic activity of estrogenic substances in the human being. Because of the experimental production of mammary carcinoma and carcinoid processes in the cervix and vagina, estrogenic therapy in the human being is looked upon by some as a possible factor in increasing the probability of cancer. Such deductions are illogical for various reasons, one of the most important being that of dosage and duration of treatment. In Lacassagne's experiments, estrone benzoate in huge doses, approximately 1/200,000 of the body weight of the mouse, was injected weekly, begun shortly after birth and carried on nearly throughout the life of the animal. A corresponding dosage in a patient weighing 132 pounds would be 0.3 gm. of crystalline estrin or 3,000,000 I. U. at one dose, begun early in childhood and continued for several years.

Cramer and Horning state in the summary of their work with estrin that "the carcinogenic changes here described were produced by the administration of estrin over a period representing a considerable fraction of the normal span of life of a mouse and corresponding in man to a period of seven to ten years, while the therapeutic administration of estrin preparations in man is, in skilled hands, limited to short periods of a few weeks or months. The development of mammary cancer described in this paper should not, therefore, be used as an argument against the therapeutic application of estrin preparations."

I believe that the majority of physicians are in accord with this above statement and that the therapeutic application of estrogenic substances in the human being has practically no carcinogenic properties.

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—Dr. Emge has used transplantable adenofibromas and has observed their behavior when growing in a single pure strain of rats under various hormone conditions produced by injection. We have been working on a similar problem but have taken two contrasted strains of mice, one of a high tumor incidence and one of low incidence. In this way we have been able to observe the behavior of spontaneous tumors growing in animals of apparently different endocrine constitution.

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DISCUSSION

DR. J. MASON HUNDLEY, JR., BALTIMORE, MD.—Dr. Emge's observations on the changes produced in the mammary gland by long-continued injections of estrogen present many interesting facts, the most interesting to me being the relation between carcinogenic and estrogenic substances, and especially whether or not the estrogens used in the human being are likely to produce malignancy. Stimulated by the pioneer work of Yamagiwa and Ichikawa in 1915, when they showed that long-continued applications of tar to the ear skin of rabbits produced cancerous changes in the tissues, there has accumulated much information concerning carcinogenesis. It has been shown by Kennaway and Cook that the compounds in coal tar responsible for the reproduction of cancer are various hydrocarbons, the most powerful being methylcholanthrene. According to Loeb they may initiate cancer formation without first causing local irritation. It has also been shown that these carcinogenic substances are related chemically to cholesterol, bile acids, ergosterol and especially to the male and female sex hormones, all of these including the carcinogenic substances containing the phenanthrene ring.

The relationship between the estrogens and carcinogenic substances is of great interest, especially in regard to the estrogenic potency of carcinogenic hydrocarbons and the possible carcinogenic activity of the estrogenic hormones. Loeb states that in comparing these two series of compounds one may conclude that there are substances which are both carcinogenic and estrogenic; that there are carcinogenic substances which are not estrogenic and that there are estrogenic substances which are not carcinogenic.

Observing the marked proliferative effect of epithelium initiated by the prolonged injection of estrogens, a study of the carcinogenic properties of these substances has been undertaken by many investigators. The major portion of this investigative work has been carried out on selected strains of mice which developed spontaneous adenocarcinoma of the breast in variable proportions, appearing in 100 per cent of cases in certain strains and not at all in others. This incidence of development applies to the female, for rarely does such a growth occur in the male breast.

Somewhat similar work has been performed by Lacassagne, Gardner, Burrows and others, but these workers have been interested especially in the relative incidence of cancer development. We on the other hand have been concerned with the precancerous changes, and especially their morphologic resemblance to the lesions occurring in the human disease known as chronic cystic mastitis.

These four gross mounts (Figs. 1 to 4) of mammary glands were all taken from animals six months of age. The first pair represent the contrasted morphology of the cancer-resistant and cancer-susceptible strains at the age of six months. You will note that the mammary gland of the resistant strain is much simpler and possesses almost no acini (Fig. 1), whereas the cancer-susceptible strain shows numerous lateral branches or alveoli (Fig. 2). These differences probably represent the earliest manifestation of the tendencies which lead to carcinoma in one animal and the freedom from it in the other.

The second point to be made is the effect of the injection of an estrogenic substance into these animals with different hereditary tendencies. This contrast is exhibited in the second pair of gross mounts. Both animals have been injected with an estrogenic substance for four months. One shows an enormous alveolar development (Fig. 4) while the other shows almost no response (Fig. 3). There is thus in addition to a structural difference developing spontaneously, a difference in the reactivity of the mammary glands to the injection of these hormones.

From these experiments which we have repeated with many animals, we can draw certain tentative conclusions. By all odds the most important factor in the development of mammary carcinoma in mice is this inherent constitutional factor. The addition of estrogenic substance simply emphasizes this difference. If one may make any inference as to the risk of giving estrogenic substances to women, one might expect that, if there is already a constitutional predisposition to mammary carcinoma in a certain woman, there may be a slight increase in the risk by giving her estrogenic therapy, whereas the woman who has no such constitutional predisposition is unaffected.

DR. EMGE (closing).—The nearest our experimentation comes to simulating the proliferative activities of mammary tissue in the human being is in the behavior of the ducts which suggests that type of hyperplasia commonly called Schimmelbusch's disease. In laboratory experimentation it has, however, been shown repeatedly that in certain strains and species of mammals, mammary tissue is incapable of exceeding certain limits of hyperplasia regardless of the amount of estrogenic hormone administered. This process must not be confused with the unlimited proliferation typical of malignancy.

It is to be expected that a constant stimulation by estrogen will create an exaggerated response in those tissues normally dependent upon this type of priming. It is important to realize that the extent of hyperplasia is predetermined and probably controlled by the same mechanism which governs cell growth. If this mechanism is defective, unusual hyperplasia may occur, provided the cells of the tissue affected possess the capacity for unusual hyperplasia. Somatic factors and hereditary susceptibility are therefore intimately related. Probably there are a number of other factors such as species, strain, and organ differentialities which further modify supernormal cell growth.

The studies presented here are preliminary to a more extensive investigation, the results of which we hope to report a year from now. Accepting that certain strains of lower mammals are hereditarily destined to grow mammary cancer, it is not surprising that an estrogenic hormone may accelerate this process. However, this does not prove that estrogenic hormones are carcinogenic agents in a broader sense, particularly in the human being.



Fig. 1.

Fig. 1.—Mammary gland of untreated mouse of the cancer-resistant strain, aged 6 months.

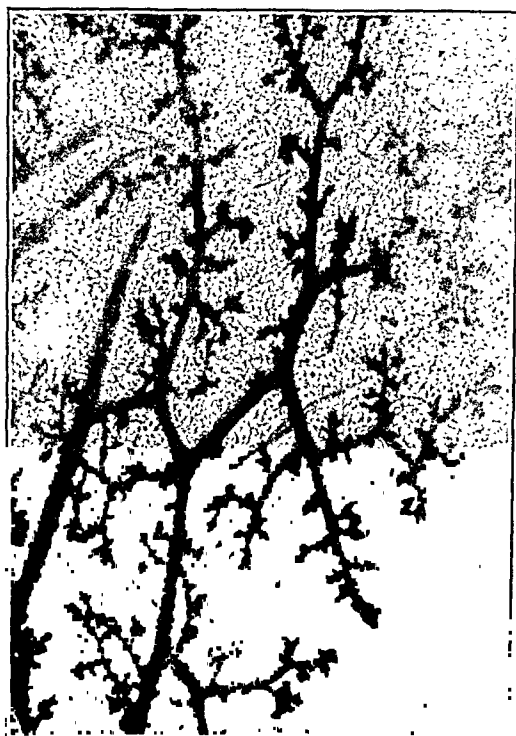


Fig. 2.

Fig. 2.—Mammary gland of untreated mouse of cancer-susceptible strain, aged 6 months.



Fig. 3.

Fig. 3.—Mammary gland of mouse of cancer-resistant strain, aged 6 months, after four months' injections of estrone.



Fig. 4.

Fig. 4.—Mammary gland of mouse of cancer-susceptible strain, aged 6 months, after four months' injections of estrone.

It seemed possible that quantitation of the two estrogens which have been identified in human urine, namely, estrone and estriol, might yield more information than the determination of total estrogen. Consequently, a cycle was followed in which the total estrogen was separated into estrone and estriol fractions, which were then assayed.⁴ It was noted that estriol reached its highest level during the luteal phase and practically disappeared at menstruation, at which time nearly all the estrogenic potency of the urine was in the estrone fraction.

This association of increased excretion of estriol with luteal activity, and vice versa, had been anticipated because of Pincus' and Zahl's

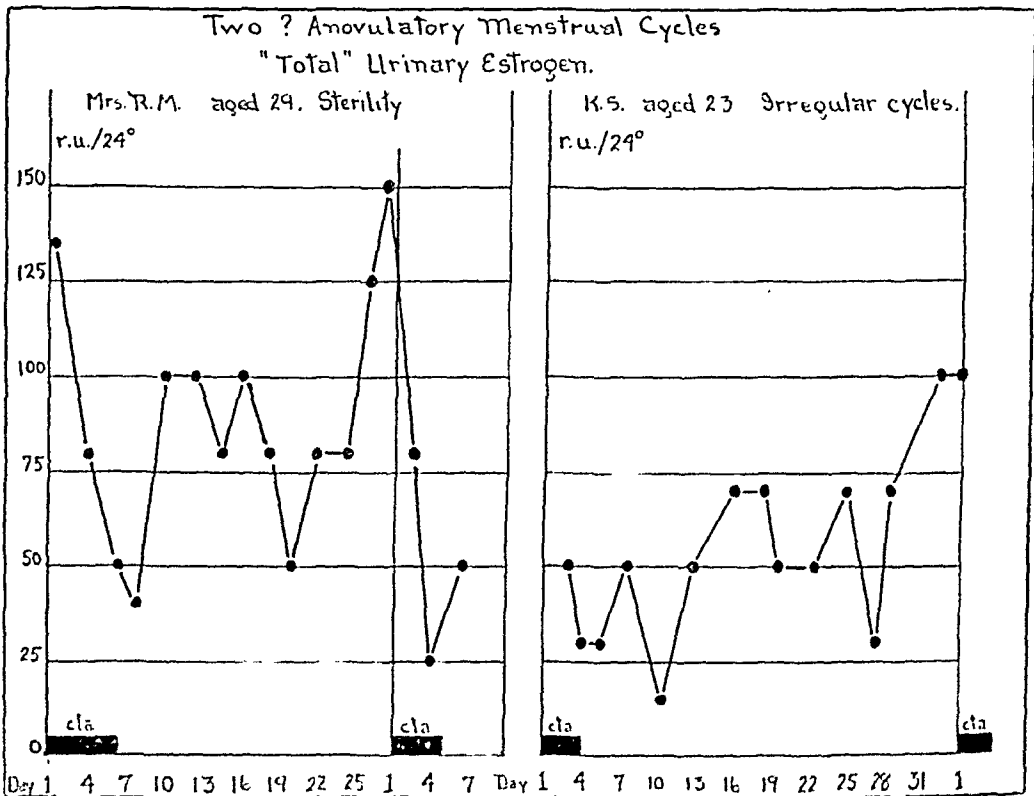


Chart 1.

experiments with rabbits^{5, 6} in which they had determined the urinary excretion of estrone and estriol under various conditions after the injection of known amounts of estrone, estriol, and estradiol. Their findings indicate: (1) that estradiol (which, according to MacCorquodale, Thayer and Doisy,⁷ is in all likelihood the primary ovarian estrogen) is converted into estrone by rabbits with ovaries and that this reaction is reversible—chemical evidence also demonstrates the reversible nature of the estradiol to estrone conversion;⁸ (2) that estrone is converted into estriol when the uterus is present and under ovarian control, this conversion being irreversible and greatly facilitated by luteal secretion; and (3) that progestin partially protects these three estrogens against destruction, thus permitting both utilization and ex-

OBSERVATIONS CONCERNING THE METABOLISM OF ESTROGENS IN WOMEN*

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ONE of the characteristics of sex hormones which differentiates them from other internal secretions lies in the fact that they are excreted either in the same forms as presumably occur in the blood or in forms definitely recognizable as metabolic products. Quantitating these factors in the urine, even with still inadequate methods of extraction and with only approximately correct bio-assay, is gradually yielding more information regarding normal and pathologic situations.

INTRODUCTION

The metabolism of estrogenic hormones by women first engaged our attention when we noted that their oral administration resulted in detectable (with the methods then available) increased urinary excretion only during the luteal phase of the cycle.¹ A role of progesterin in the excretion of estrogens had previously been indicated by experiments with rabbits, namely, that injected estrone could be recovered in fair quantities in the urine of ovariectomized does only if progesterin were simultaneously administered.²

With improved methods quantitation of total urinary estrogen throughout normal menstrual cycles demonstrated a peak of excretion early in the period of luteal activity with low levels just before menstruation and during follicle ripening.³ The most conclusive evidence that this type of curve represents a normal ovulatory cycle is the fact that two women, studied before and during the month of conception, showed exactly this curve of excretion to the twenty-fifth day.³ The drop in estrogen before flow is in keeping with the "estrogen-withdrawal" theory of menstruation.

In four instances (two of which are shown in Chart 1) thus far, curves of total urinary estrogen lacked the characteristic intermenstrual peak and, furthermore, rose before the onset of bleeding. They are assumed to represent anovulatory cycles. The high level at the start of flow argues against the "estrogen-withdrawal" theory.

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excretion of estriol increased at a more rapid rate than that of estrone, resulting in constantly higher ratios of estriol to estrone. In the urine of pregnancy, Browne, Henry and Venning have quantitated pregnandiol glucuronidate¹⁰ and have found a constant increase of this excretion product of progestin with advancing gestation, this indicating progressively greater secretion of progestin. Here again, as in the menstrual cycle, urinary estriol is apparently a gauge of the amount of progestin. Preceding delivery estriol excretion dropped off markedly, and there was a concurrent augmentation of the potency of the estrone fraction, which comparison of colorimetric assay with bio-assay indicated was due to some estrogen other than estrone. These findings, analogous to those at menstruation, suggest that in the initiation of labor, as in the initiation of menstruation, progestin deficiency in the presence of estrogen production may result in a changed metabolism of estrogens and the consequent action of a positive precipitating factor. In the determination of "total" estrogen at the time of delivery, any rise in the estrone fraction would be completely marked by the drop in estriol. In the paper⁴ in which the above material was first reported we predicated that the hypothetical positive factor might actually be estrone. Further consideration of the known facts about endometrial bleeding and delivery, however, and the investigations to be presented below lead us to believe that the rise in the estrogenic potency of the estrone fraction at the time of these processes may be an indication of the action of a positive factor but not "the positive factor" itself.

FURTHER OBSERVATIONS CONCERNING THE METABOLISM OF ESTROGENS

At this point it is pertinent to point out that, although estrone and estriol have been obtained in crystalline form from the urine of pregnant women, there is no proof that they are the only estrogens excreted during pregnancy. Furthermore, the urinary estrogens of the nonpregnant have not been isolated and identified, but, on the basis of consistent findings, we have assumed them to be estrone and estriol. In order to test further the method of hydrolysis (Smith and Smith) and separation (Cohen and Marrian) used in these investigations, we have added pure estrone, estriol, and estradiol* in varying proportions to 100 to 700 c.c. amounts of urine from nonpregnant women, the titration values of which were simultaneously determined. Estrone, due to its ketonic nature, combines with semicarbazide hydrochloride to form a biologically inert semicarbazone.¹¹ Neither estriol nor estradiol has this property. By semicarbazide treatment, then, it can be discovered whether or not any estrone is present in estriol fractions, or any nonketonic estrogen in estrone fractions. These recovery experiments have demonstrated that crystalline estrone, estriol, and

*We wish to express our gratitude to the Schering Corporation, which, through Dr. Gregory Stragnell and Dr. Erwin Schwenk, has supplied us not only with the above substances but with large quantities of specially prepared proluton (progesterone) and progynon-B (estradiol benzoate) for clinical trials.

cretion, there probably being no renal threshold. Based on these observations, and our own, in women, the schematic representation of the metabolism of the estrogens given in Chart 2 has been evolved.

Relatively high levels of estriol excretion, then, during what was presumably the luteal phase of the cycle suggest that in women, as in rabbits, excretion of estriol may be taken as a gauge of secretion of progestin. Thus would the marked drop in estriol two days before menstruation signify regression of the corpus luteum. This interpretation is strengthened by the work of Venning and Browne⁹ who find that pregnandiol glucuronidate, the excretion product of progestin, disappears from the urine one to three days before the beginning of

Metabolism of the Estrogens

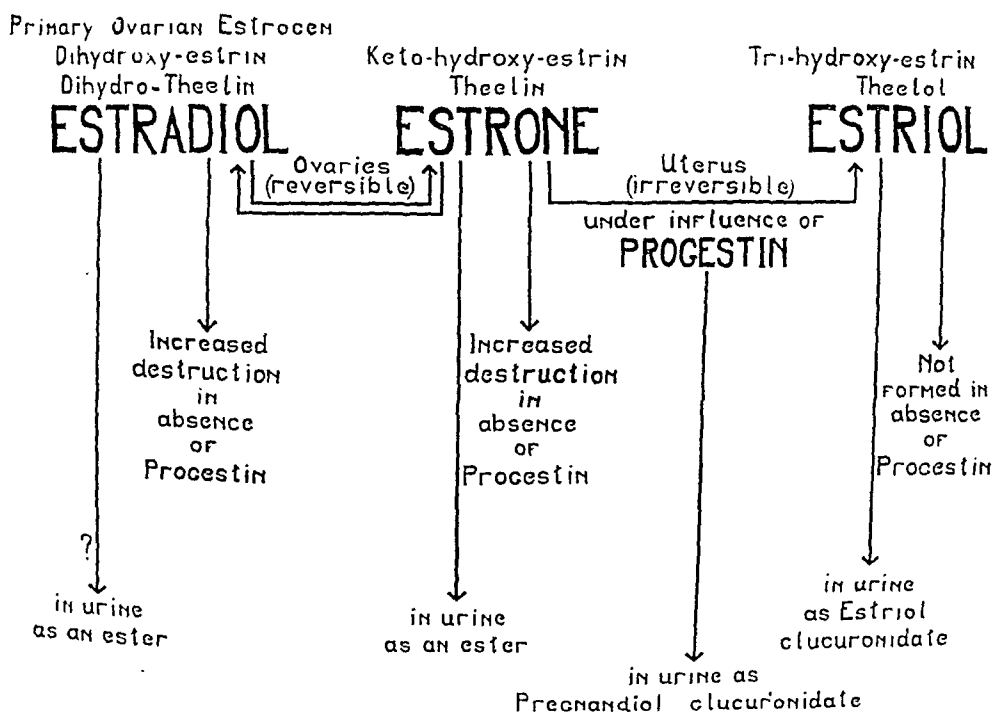


Chart 2.

flow. With the onset of menstruation there was a further drop in estriol and a rise in the potency of the estrone portion, so that the ratio of estrone to estriol during the first two days was much higher than at any other time in the cycle. This observation has been confirmed in another normally menstruating woman (*v.i.*) and is sufficiently definite to suggest that something more than a withdrawal phenomenon may be concerned in the initiation of normal menstruation, just as the increase in estrogen excretion at the time of anovulatory flow may be construed as reflecting some positive influence. In measuring "total" estrogen in normal cycles, this estrone rise would be masked by the drop in estriol.

Throughout a normal pregnancy also were urinary estrone and estriol determined.⁴ From the time of the second missed catamenia

With the beginning of flow, however, estriol reaches its lowest level and there is a threefold increase of "x" estrogen, estrone itself being entirely absent. We believe this shift in excretion of estrogen at menstruation to signify the growth of a new ovarian follicle (a process known normally to follow upon reduced activity of the corpus luteum) with increased production of estradiol. Progesterin being deficient for the amount of secreted estrogen, there is but little conversion to estriol. A failure in conversion would result in a higher concentration of estrone and estradiol, both of which factors are rapidly destroyed in the absence of progesterin. In fact, whatever estrone is

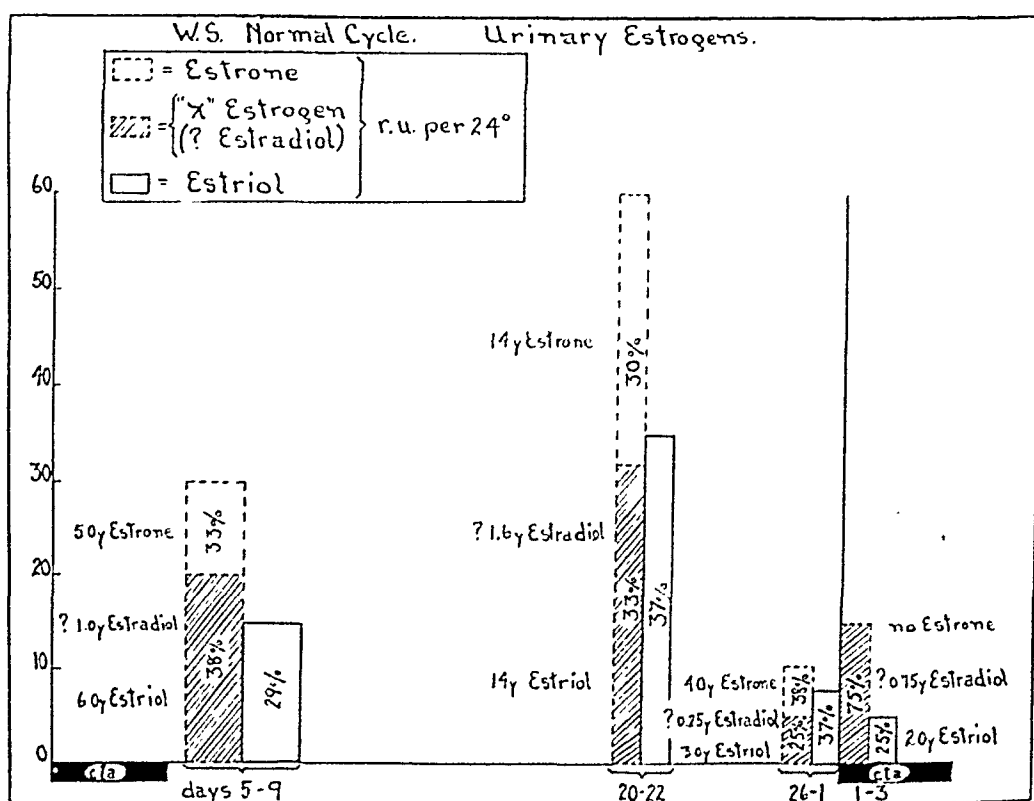


Chart 3.

Erratum: Days 5 through 9 of normal cycle: Estrone should be 22.5 per cent; "x" estrogen should be 44.5 per cent; estriol should be 33.0 per cent.

not converted to estriol or back to estradiol is so rapidly destroyed that none can be detected in the urine. We are led to wonder whether concentration in the endometrium of nonestrogenic, possibly toxic, sterols resulting from estrogen destruction may not be concerned in the local vascular phenomena which are involved in menstruation. By this thesis both ovulatory and anovulatory flow could be explained, viz., production of estrogen in the face of deficient or absent progesterin with a resultant shift in the metabolic chain of events, giving breakdown products of estrone and estradiol instead of estriol, and consequent flow, providing the endometrium is sufficiently proliferated.

estradiol are not destroyed by the hydrolysis, that separation of estrone from estriol is complete and that estradiol is entirely taken over into the estrone fraction.* If these three should be the only estrogens elaborated by women, it may be concluded that the potency of estriol fractions is entirely due to estriol, whereas the potency of estrone fractions may be due to estrone and/or any estradiol that escapes into the urine prior to conversion or destruction. Since estradiol is 10 times as strong estrogenically as estrone, even minute amounts of it would significantly raise the activity of estrone fractions. As mentioned above, comparison of colorimetric with bio-assay⁴ gave evidence for the presence of some estrogen much more active than estrone in the urine of late pregnancy. Treatment by semicarbazide of the estrone fractions of urines from both pregnant and nonpregnant women has given further evidence for the excretion of some estrogen other than estrone and estriol. It seems reasonable that this third factor is estradiol, but, lacking direct proof, we shall refer to it as "x" estrogen.

NORMAL MENSTRUAL CYCLE

We have not yet been able to perform estrone-estriol separations together with semicarbazide treatment of the estrone fractions throughout a normal menstrual cycle. On four specimens from one individual, however (Chart 3), this procedure has been followed. Based on a calendar record, the individual's cycles never vary from twenty-eight days by more than twenty-four hours. The specimens were collected as follows: one during the follicular phase, one during the luteal phase, the third for the forty-eight hours preceding menstruation, and the last for the first two days of flow. The findings agree with those already published and go further in showing that a large proportion of the potency of the estrone fraction is accountable to "x" estrogen. If the results are expressed in micrograms rather than in rat units and the "x" estrogen assumed to be estradiol, it is evident that this substance is excreted actually in very small amounts by weight. Its presence in all these specimens would signify that at no time in the cycle is the estradiol to estrone to estriol conversion complete. Most conversion, judging by the percentage of estriol excretion, appears to take place during the second half of the cycle, as would be expected. During the last two days, despite low total estrogen, the percentage of estriol remains unchanged, indicating that a metabolic balance between estrogen and progestin is still being maintained.

*All values recorded in this paper were obtained by bio-assay performed according to the technique previously described.⁴ The recovery experiments reported in this earlier communication were done with 100 c.c. amounts of urine. The extraction of larger volumes apparently introduces a greater chance for loss (never more than 25 per cent). In the analysis of urines from pregnancy we routinely extract 100 c.c. per liter of the twenty-four-hour volume. It is usually necessary to extract the whole of a forty-eight-hour specimen from the nonpregnant to obtain sufficient estrogenic material for accurate bio-assay. However, since approximately equal volumes of different specimens are used, the results should be comparable despite the unavoidable loss.

well as failure of conversion. In fact, if there was any conversion to estrone, this substance was being so rapidly destroyed that none escaped into the urine.

The administration of progesterone* resulted (after the third injection) in the excretion of appreciable amounts of estrone and estriol, this constituting our first post hoc evidence for the role played by progestin in the conversion to estriol. The fact that estrone also appeared in the urine indicates, first, the effect of estriol formation in carrying the reversible estradiol to estrone reaction to the right, and second, the protective action of progesterone against estrone destruction, thus allowing excretion. Administration of progesterone also resulted in a 50 per cent decrease in the total estrogenic potency of the urine. However, if "x" estrogen is assumed to be estradiol and the urinary estrogens are expressed in micrograms rather than rat units, the excretion before progestin therapy amounts to only five micrograms and afterward to a total of 17 micrograms (10 micrograms estrone, 1 microgram estradiol and 6 micrograms estriol), indicating that conversion was accompanied by decreased destruction. This medication had no effect on the patient's flowing.

On the tenth day of the experiment (Jan. 19 and 20, 1938), injection of 10 mg. of progesterone was followed in the course of the next six hours by the injection, in two doses, of a total of 50,000 I. U. of estrone.† There was recovered on this and the following day about 16 per cent of the injected material in terms of rat units, but on differential analysis only 42 per cent of this consisted of estrone, the hormone administered, while 38 per cent was accountable to "x" estrogen and 20 per cent to estriol. Not knowing how much of the injected estrogen would have been recovered had the patient not received progesterone, it is impossible to state how much protection of estrogen progesterone afforded in this instance, although it is a fair assumption that even less total estrogen would have been recovered without progesterone. The presence of estriol means conversion. A good proportion of the estrone was also obviously changed to "x" estrogen (estradiol?). In other words, the indications are that, although sufficient progesterone was given to render partial protection against destruction of the estrogens and to cause some estrone to estriol conversion, the amount of administered estrone was more than could be efficiently taken care of by the progestin activity, since urinary studies gave evidence for considerable destruction as well as reversal of the estradiol to estrone reaction. There was no alteration in the amount of flow.

On the twelfth day (Jan. 21 and 22, 1938), 10 mg. of progesterone and 50,000 I.U. of estrone were injected together. Urinalysis for the twenty-four hours failed to reveal any estriol. Apparently the large

*Proluton, Schering Corporation.

†The oil, kindly made up for us by Parke, Davis & Co., through the courtesy of Dr. H. A. Sharp, 29,666 I. U. \approx 10,000 R. U. by our assay.

DYSFUNCTIONAL FLOWING

Quantitation of the estrogens in the urines from a patient* with dysfunctional flowing (Chart 4) has confirmed the above data and lent more plausibility to the ideas derived therefrom. This patient is a typical refractory case, aged 23, who has been under observation and various conservative treatments for four years. Frequent biopsies have consistently revealed a "Swiss cheese" endometrium. She gives a history of irregular flowing since puberty at the age of fifteen. Bouts of prolonged and excessive flowing have been interspersed with periods both of constant dark discharge and of amenorrhea lasting

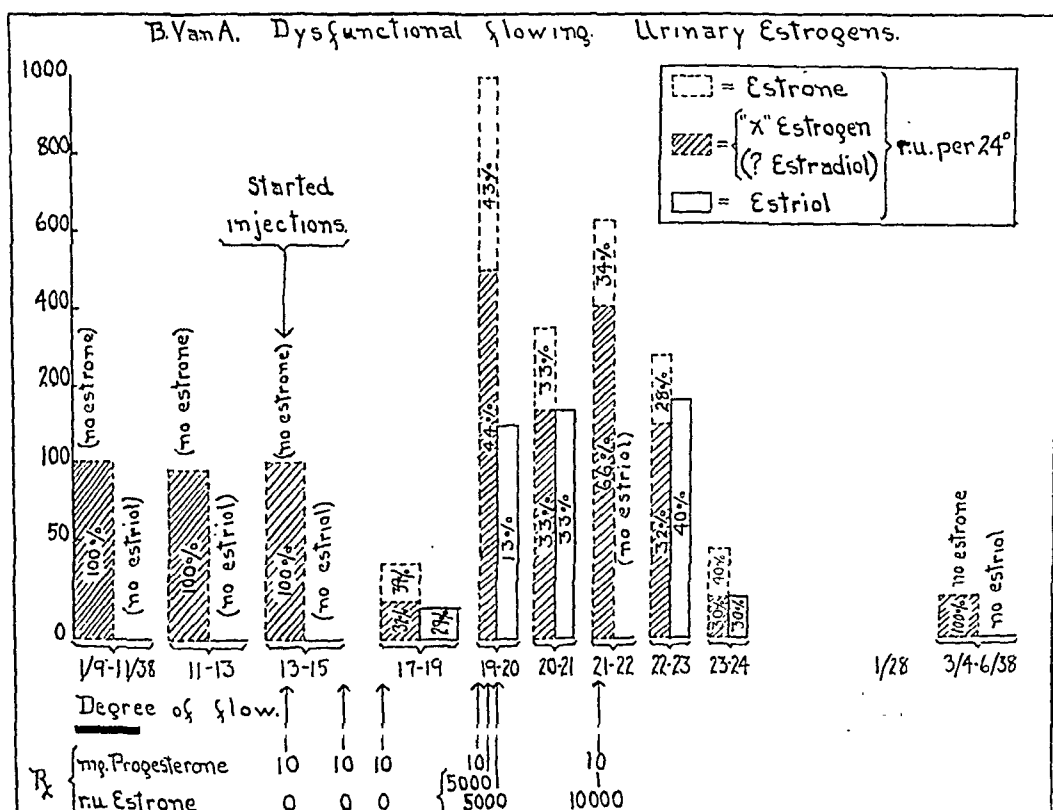


Chart 4.

three to four months. One such span of amenorrhea followed resection of a 3 cm. cyst of the left ovary nearly four years ago. At the time this study was begun she had had constant dark discharge for four months with occasional short spells of bright flow with clots. She was put to bed and placed on constant urinary drainage. For the four days preceding injections the urine contained comparatively high estrogenic activity, all accountable to "x" estrogen (estradiol?). This signifies to us such rapid secretion that goodly amounts were being spilled over into the urine. No estrinol was detected, indicating, as would be expected in this patient, a uterus completely lacking luteal control. Lack of progestin involves increased destruction as

*We are indebted to Dr. John Rock for essential cooperation in the study of this case.

leled by the percentage of estriol in the urine. Furthermore, they indicate that a deficiency of progestin pertains at the time of the clinical manifestation of late pregnancy toxemia and eclampsia, the actual evidence being low urinary pregnandiol and estriol, as compared with normals, and a decreased ratio of estriol to the potency of the estrone fraction, due either to low estriol alone or to both low estriol and excessive activity in the estrone fraction. Weil¹⁵ has also reported that the values for urinary pregnandiol in cases of toxemia of pregnancy are below those for normal pregnancy.

In a limited number of specimens so far the potency of the estrone fractions has been measured before and after treatment with semi-

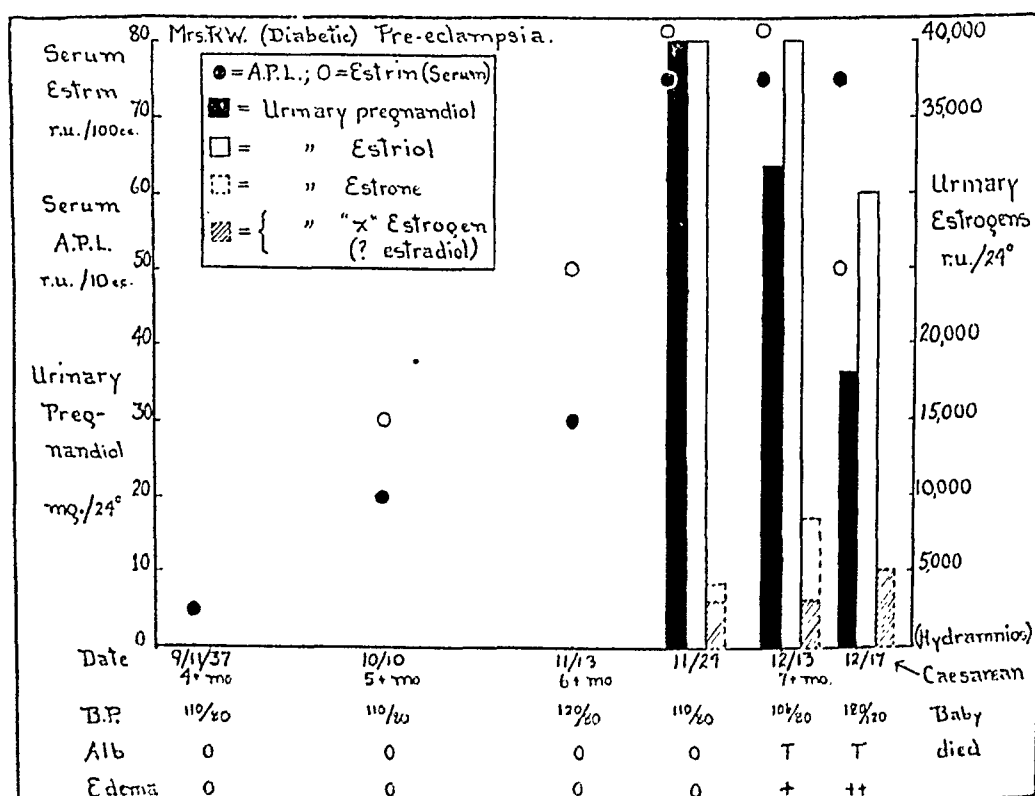


Chart 5.

carbazide. One patient, a diabetic (Chart 5), was studied prior to the development of pre-eclampsia. The first urine was collected because of the abnormal rise in serum anterior pituitary-like substance (prolan, anterior pituitary-like substance), which led us to anticipate trouble.¹⁶ Clinically the patient was still progressing through a normal gestation and the first values for pregnandiol, estrone, estriol, and "x" estrogen were within the limits of normal. Three weeks later another urine was obtained, the patient having developed some edema and albuminuria. Pregnanadiol had dropped; estriol had not risen. Estrone excretion, however, had increased and semicarbazide treatment revealed the augmentation to be due to estrone and not "x" estrogen. These analyses signify to us increased elaboration of estrogens, as is normal with ad-

doses of estrone had temporarily prevented the progesterone from influencing the uterus, just as Allen¹² demonstrated in rabbits and Zuckerman¹³ in monkeys, thereby inhibiting conversion to estriol. Failure of conversion would necessarily (according to our theory) involve increased destruction, and this was clearly the case, since considerably less total estrogen was recovered following this injection of 50,000 I. U. than during the twenty-four hours after the previous similar treatment. It seems significant that the patient had a twelve-hour spell of bright flow during this time of rapid destruction. Forty per cent of the estrogenic activity of the next twenty-four-hour specimen (Jan. 22 and 23, 1938) was due to estriol, the interpretation being that, through destruction and excretion, there was sufficient decrease of estrogen to allow progesterone to act. Flowing ceased completely during this time. On the fourteenth day (Jan. 23, 1938), two days after the last injection, one of the severest bouts of flowing occurred that the patient had ever experienced, lasted three days, then diminished and stopped completely by Jan. 28, 1938. The specimen collected during the first twenty-four hours of excessive bleeding was similar in amount and kind of estrogen to that preceding the estrone injections. Since it is apparent that very large amounts of estrone were being destroyed between the nineteenth and twenty-third of January, it is tempting to postulate that the ensuing flow was due to a greater concentration of breakdown products involving more endometrium.

There has since been no "show" whatsoever (as of May 25) and a twenty-four-hour specimen early in March was low in total estrogenic potency, all of the activity present being accountable to "x" estrogen (estradiol?). We would conclude that this patient's ovaries are still completely lacking in luteal activity, and that bleeding will begin again as soon as the endometrium shall have sufficiently proliferated to respond to whatever effect is associated with a progestin-deficient metabolism of the estrogens. It is impossible to reconcile the findings in this case with the "estrin-deprivation" theory of menstruation, since, during the control period, the patient was bleeding when the urinary excretion of estrogen was at a constant level five times as high as was found during a nonbleeding phase.

TOXEMIA OF LATE PREGNANCY*

In a normal pregnancy (*v.s.*) estriol excretion appeared to reflect progestin secretion. To confirm this and to discover any abnormality in the level of progestin in patients with late pregnancy toxemia, a total of 88 specimens of urine from 18 pregnant women have thus far been assayed for estrone and estriol. Pregnandiol has also been measured¹⁴ in 64 of these. Seven of the patients had normal pregnancies, 9 had late pregnancy toxemia and 2 eclampsia. The results agree that secretion of progestin, based on urinary pregnandiol, is paral-

*We wish to acknowledge with gratitude the cooperation of Drs. Elliott P. Joslin, Frederick C. Irving, Priscilla White and Samuel B. Kirkwood in these studies.

estrogen. Clinically, however, no change for the better could be detected. It became necessary to stop therapeutic trials because of severe urticaria around the sites of injection. Three days later, coincident with a recurrence of high anterior pituitary-like substance, a decrease in urinary estriol and more activity in the estrone fraction (the changes in estrogens being of the same sort as described above [see "Introduction"]) in the urine of a patient at the time of normal delivery), mild spontaneous labor started, the membranes were ruptured and twins delivered. Four convulsions occurred during the subsequent sixteen hours. Both mother and infants were well six weeks later.

This case demonstrated two important points: first, that therapy with progesterone and estrogen, with the kinds and amounts administered, had no immediate or dramatic effect upon the severe pre-eclampsia; second, that the medication not only did reduce anterior pituitary-like substance but raised serum estrogen and changed the urinary estrogens in the direction of a normal balance. It is only fair to state, however, that conclusions based on the data derived from urinary studies in a case of this sort can be only approximately correct, since there was a considerable element of error introduced by the presence of much albumin, which renders extraction and separation less satisfactory.

Another patient, a diabetic, who had had pre-eclampsia with her previous pregnancy and had delivered a macerated fetus (Mrs. Wh., Charts 5 to 8),¹⁶ was treated at the onset of mild toxemia (albumin, slight trace; edema, +) at seven and one-half months, when pregnandiol had dropped 50 per cent and urinary estrogen was extremely low. For the previous four weeks serum anterior pituitary-like substance had been found to be increasing. Over a period of two weeks she received 140 mg. of progesterone and 1,650,000 I. U. of estradiol benzoate. During this time her blood pressure fluctuated from 120/80 to 150/110 and albumin from nothing to a trace. There was a negligible amount of edema. At the eighth month she was delivered. Mother and infant did well.

With the injections anterior pituitary-like substance fell to normal (100 R.U./100 c.c. serum), serum estrin rose and both pregnandiol and estriol in the urine increased markedly, the potency of the estrone fraction remaining down. In other words, the balance was thrown well toward normal.

The question that cannot be answered in this instance is whether or not medication, administered at the onset of early manifestations, warded off a more serious situation, even if it did not bring about a complete return to normal clinically. (On the day before delivery the blood pressure was 120/80, there was the slightest possible trace of albumin and edema was barely detectable.)

A third "pre-eclamptic," a primipara, aged 28 years, who, over a period of nine days, received 170 mg. of progesterone and 2,550,000 I. U. of estradiol benzoate, showed no clinical change whatsoever and

vancing pregnancy, but reduced conversion of estrone to estriol, which is consistent both with reduced progesterin (based on urinary pregnandiol) and failure of a rise in estriol.

Four days later the patient's blood pressure suddenly went up and edema was more pronounced. Urinalysis revealed less pregnandiol and estriol and complete disappearance of estrone, the activity of the estrone fraction being accountable entirely to a rise in "x" estrogen. These shifts in excreted materials are quite comparable with those which occur at the time of menstruation and constitute evidence for an analogous situation, namely, production of estrogen in the face of a deficiency of progesterin with resultant inadequate conversion and greater destruction. Is it possible that the vascular phenomena of pre-eclampsia may be precipitated by the same changes in estrogen metabolism that occur at menstruation? Again it is tempting to postulate that an increased concentration of estrogen breakdown products is concerned. "Toxemia" may be the correct term after all.

TOXEMIA OF LATE PREGNANCY TREATED BY ESTROGEN AND PROGESTERONE—PRELIMINARY REPORT

The employment of estrogen in late pregnancy toxemia was rationalized by the finding of low levels of estrogen and high anterior pituitary-like substance in the serum and urine of patients with this syndrome.^{*16} Since these two hormones seem to be mutually antagonistic (high anterior pituitary-like substance almost invariably being associated with low estrogen and vice versa), administration of estrogen appeared to be the logical way to re-establish a balance. We have in fact found, in six cases now, that injection of estrogen alone was followed by a lowered titer of anterior pituitary-like substance. Even massive doses, however, have failed to raise the level of serum estrogen. Our more recent investigations offer an explanation for this, namely, that these women were not secreting enough progesterin to protect the additional estrogen against destruction. This consideration, strengthened by the finding of low urinary pregnandiol, makes therapy by estrogen *plus* progesterin a more reasonable procedure to follow in the hope of re-establishing a normal hormonal balance in toxemia of late pregnancy.

A patient with severe pre-eclampsia in the seventh month was the first to receive a trial of this therapy. At the time neither pregnandiol nor "x" estrogen was being quantitated, but the anterior pituitary-like substance of both serum and urine was strikingly high and the urinary estrogens were low, there being, however, in the estrone fraction an abnormally large proportion of the estrogenic activity. Four days of treatment with a total of 25 mg. of progesterone† and 750,000 I. U. of estradiol benzoate‡ resulted in a shift of the anterior pituitary-like substance estrone and estriol toward normal. There was also a rise in serum

*Actually, to May, 1938, 70 out of 80 patients diagnosed as having pre-eclampsia and eclampsia, and studied by us, had this imbalance.

†Proluton.

‡Progynon-B, Schering Corporation.

DISCUSSION

In the interpretation of the data presented it has been theorized that a positive precipitating factor associated with a progestin-deficient metabolism of the estrogens may be responsible for both endometrial bleeding and late pregnancy toxemia. We realize that this hypothesis is not entirely justified on the basis of the actual findings. If total estrogen alone is considered, the data on normal cycles are entirely in keeping both with the progestin- and estrin-withdrawal theories of menstruation. However, in the cycles in which estrogen rose at the time of flow, and in the case of dysfunctional flowing in which five times as much total estrogen was being excreted at the time of bleeding as was found in the nonbleeding phase, it would seem that estrin withdrawal cannot apply. For this reason and because of the evidence for a striking change in estrogen metabolism at the time of both types of flow from that found in the intermenstrual period of a normal cycle, it is tempting to postulate that some factor associated with or produced by this changed metabolism may actually be the direct cause of endometrial breakdown. Inasmuch as the partition of the urinary estrogens when bleeding occurs, and also in toxemia, is indicative of increased destruction, one is naturally led to theorize that breakdown products may be responsible.

Certain observations in connection with the production of experimental endometrial bleeding are difficult to reconcile with this hypothesis, e.g., the latent period and the inhibition of bleeding by maintaining a sufficiently high dose of estrogen.

Regardless of the interpretation of the results, it is evident that a marked change in the metabolism of estrogens takes place at the time of menstruation and at the appearance of clinical signs in late pregnancy toxemia. Furthermore, this change would not have been detected had we limited ourselves to the determination of "total" urinary estrogen.

SUMMARY AND CONCLUSIONS

Estrone and estriol have been quantitated (1) in 4 specimens of urine from a normally menstruating woman at crucial times in the cycle; (2) in 10 urines from a patient with dysfunctional flowing—during a control period, after progesterone and after progesterone and estrone; and (3) in 88 urines from 18 cases of late pregnancy, 7 normal, 9 toxemic, and 2 eclamptic.

An as yet unidentified ("x") estrogen, presumed to be estradiol, has also been quantitated in the specimens from the woman with normal catamenia, from the patient with dysfunctional flowing and from one of the patients with pre-eclampsia, who was studied before and after the appearance of signs.

Pregnandiol has been measured in 64 of the urines of pregnancy.

had a spontaneous delivery late in the eighth month, four days after the last injection. In contrast with the others, however, the anterior pituitary-like substance of serum and urine on two occasions shortly before treatment was normal, as were also urinary pregnandiol, estriol, and estrone. This constitutes the tenth case that we have studied in which a clinical diagnosis of pre-eclampsia failed to be associated with the typical hormonal imbalance. In nine other cases, definitely diagnosed as nephritic, normal values for serum anterior pituitary-like substance were found. As Kellogg¹⁸ suggests, determination of anterior pituitary-like substance may find a place as a test for the presence or absence of true pre-eclampsia. Regardless of the diagnosis, one would expect no benefit from endocrine therapy in a situation with no demonstrable hormonal abnormality.

Three other patients, diabetics, have been treated similarly on the basis of raised serum anterior pituitary-like substance between the fifth and seventh months. None of them had developed any clinical evidence of toxemia at the time medication was begun, in the seventh month. The urinary studies are not finished and will be reported later in detail. All three patients progressed through uneventful pregnancies to within three weeks of term and were then delivered of vigorous, well babies. This type of therapy, given early, would seem to offer promise of clinical success.

The results of such preventive measures are difficult to evaluate. In the course of the last five years, however, we have assayed for anterior pituitary-like substance 520 serums from 164 women. There were no normal pregnancies among the 78 cases with high serum anterior pituitary-like substance. Moreover, of 28 women in whom an abnormal augmentation of serum anterior pituitary-like substance was discovered between the fifth and seventh months, 21 developed toxemia of varying degree four to six weeks later and the other seven had spontaneous premature deliveries. We are inclined to the opinion, therefore, that treatment was successful in the last three cases, although many more such outcomes will be required to constitute incontrovertible evidence.

It is difficult to understand why excessive anterior pituitary-like substance, a hormone whose characteristic property is its luteinizing effect, should be followed by a deficiency of progestin with the consequent shift in the metabolism of the estrogens. This apparent paradox calls for further study, and suggests that the high values for anterior pituitary-like substance in pre-eclampsia may possibly be due to some synergistic factor rather than excessive production of anterior pituitary-like substance itself. A pituitary synergist has been ruled out by previously reported tests on hypophysectomized rats.¹⁷ We still feel that this "prolan" abnormality is somehow involved in the primary etiology of pre-eclampsia, although the present investigation would indicate that the clinical manifestations are precipitated by a situation analogous to that at the time of menstruation, viz., a progestin-deficient metabolism of the estrogens.

DISCUSSION

DR. HOWARD C. TAYLOR, JR., NEW YORK, N. Y.—Two new concepts in gynecologic endocrine diagnosis have been presented by Dr. Smith. The first of these is the estriol/estrone ratio, which is, as I understand from his presentation, normally high during the luteal phase of the cycle, low at the time of menstruation, and before labor. It is pathologically low during periods of dysfunctional flowing and in pre-eclampsia. Estriol in general is present during times of corpus luteum activity.

The second point is the demonstration of a hitherto unknown estrogen in human urine, probably to be regarded as estradiol. This "x" estrogen is found to be increased at the time of menstruation, in dysfunctional flowing and in pre-eclampsia. Its presence is evidence of low corpus luteum activity.

These observations are of importance in two directions. First, they promise a new method of investigation. Second, they have already offered new insight into conditions underlying important gynecologic and obstetric diseases.

The hypothesis that the vascular phenomena responsible for endometrial flow may be induced by toxic concentration of non-estrogenic breakdown products resulting from a destruction of the estrogens seems, however, difficult to reconcile with certain experiments producing artificial menstrual bleeding. As you know, women without ovaries have had menstruation experimentally induced by giving an estrogenic substance, and then more or less abruptly discontinuing it. It is difficult to see why this reduction in estrogenic administration should be associated with an increased destruction of estrogens.

The findings in the toxemias of pregnancy interest me particularly, because we have been carrying on somewhat similar investigations recently at the New York University Medical School. In general we agree with Dr. Smith on his previously reported findings of low total estrogens and on his report today of a lowered pregnandiol. We have not attempted the separation of the three different estrogenic substances.

Many reasons combine to make me hesitant in reaching conclusions on this subject.

First, in our experience it has been extremely difficult to fix the normal values for estrogenic substance in the urine of pregnant women, even at a given period of gestation. The figure varies not only from individual to individual, but even in the same patient from week to week.

Second, the diagnosis of the specific toxemia of pregnancy is a very unstable one. Differences in the distribution of cases into such groups as chronic nephritis, specific toxemia and essential hypertension may profoundly affect conclusions drawn from hormone studies.

Probably the greatest difficulty is in the interpretation of the figures obtained. Are the abnormal values in the urine related to the cause, or are they simply the result of the pre-eclampsia? The amount of an estrogen excreted during pregnancy depends on three or four factors, namely:

1. The amount produced in the placenta.
2. The amount destroyed, probably in the liver.
3. The amount converted, perhaps in the uterus.
4. Possibly upon a renal threshold which may exist for the conjugated substance if not for the free estrogens.

In the determination of pregnandiol it will be remembered that the substance actually measured is sodium pregnandiol glucuronidate. If conjugation with glucuronic acid, which is probably dependent on a liver function, fails, the substance will not be detectable in the urine by present methods.

Since lesions of the placenta, kidney, and liver are recognized to occur in pre-eclampsia, is it not possible that the changes in the quantitative relationships of the estrogens in the urine are the result of renal, placental, or hepatic disorders and are not related to the underlying cause of eclampsia?

Physiologically the determinations, confirming and enlarging upon Pincus' studies with rabbits, indicate:

1. That estradiol is convertible into estrone and estrone into estradiol.
2. That progesterin, acting through the uterus (probably the endometrium), brings about the conversion of estrone to estriol, thus carrying the estradiol to estrone reaction to the right. Accordingly, the distribution of the estrogens in the urine supplies an index of progesterin activity.
3. That progesterin partially protects the estrogens against destruction, thereby allowing greater utilization and excretion. The amount of estrogen in the urine represents the balance between production and destruction.
4. That deficiency of progesterin, therefore, results in (1) reduced conversion of estrone to estriol, (2) thus causing the estradiol to estrone reaction to swing to the left, and (3) greater destruction of all estrogens.

Clinically the determinations indicate:

1. That endometrial bleeding is associated with both increased production and increased destruction of estrogen, which processes accompany a state of progesterin deficiency, and that this situation is exaggerated in dysfunctional flowing.
2. That the manifestations of pre-eclampsia coincide with changes in the urinary values for pregnandiol, estrone, estriol, and estradiol which reflect a progesterin-deficient metabolism of the estrogens.

It is postulated that the vascular phenomena which are responsible for endometrial flow and pre-eclampsia may be brought about by a toxic concentration of nonestrogenic breakdown products, resulting from destruction of the estrogens.

A preliminary report is included on the treatment of pre-eclampsia with large amounts of progesterone and estradiol benzoate. Thus far it appears that such therapy shifts the progesterin-estrogen balance in the direction of normal and offers some promise of value, provided injections are started sufficiently early.

We are indebted to Miss Sara Schiller for valuable technical assistance in this investigation.

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Our reason for postulating that breakdown products of estrogen destruction may be concerned in the arteriolar spasm of these states is based on the following: experimental endometrial bleeding has been produced both in monkeys without ovaries and hypophysis and in monkeys without ovaries and adrenals.

Apparently all that is needed for flowing is a live monkey with an endometrium that has been under the influence of estrone. Although necessary for endometrial bleeding, estrone itself is not the actual cause of the bleeding. Our line of thought has been that the bleeding factor, which we are convinced must exist, is due to something that estrone does or something that is done to estrone, or possibly both. And since estrone disappears in the face of increased estrogen production at the time of menstruation and at the onset of pre-eclampsia, we are guessing that its destruction yields the responsible factor.

Dr. Taylor raises the question as to whether the pathology of pre-eclampsia may not be the cause rather than the result of the changed metabolism of estrogens, and suggests the possibility that the conjugating mechanism of estrogen and progestin may be consequently upset. We feel that one would expect in that case much more marked disturbances in the blood and urinary chemistry. Furthermore, our observations indicate an actual deficiency of progestin in this disease, not only on the basis of urinary pregnandiol but also on the basis of urinary estrone, estriol and "x" estrogen.

The reason we have used estrogen in therapeutic trials is because it depresses the high serum anterior pituitary-like substance. Speaking of this substance raises a point regarding discrepancies in the results of assay. Neither Dr. Taylor nor Dr. Ross has confirmed our finding of high anterior pituitary-like substance in toxemia, and I wonder if this is not due to their use of urine for assay instead of serum, since there is so much more chance for error in the collection as well as the assay of urine.

One question I would like to ask in regard to the theory of treatment, and that is why should one give both estrogen and progesterone in cases of pre-eclampsia? Would not the progesterone alone be as effective in reducing the supposed estrogen destruction?

DR. R. A. ROSS, DURHAM, N. C.—Since the work of Brown and Venning, Hamblen has been working on the metabolism of progestin. We feel that pregnandiol is a test of the utilization of progestin. This is based on the fact of a decrease in its output in a woman who is bleeding or if the endometrium is removed by curettage or if the uterus is removed and the ovaries remain intact. These findings are of special interest in view of what Dr. Smith has said. He has shown by a diagram the possible interplay and alteration of the sterols. Also, Hamblen has been able to recover only 65 per cent in the urine of a known injected quantity. In order to know as much as possible about these products, we must know the amount elaborated, the question of their utilization, alteration, and excretion. In a pregnant individual the fetus and its appendages, the corpus luteum of pregnancy, and the decidua all are complicating factors.

We have not been able consistently to find the alteration in the gonadotropes of the urine and blood in the toxemic patients. He has mentioned changes in the estrogen in the toxemias, and appropriately uses serum estimates as well as urine estimates.

DR. EMIL NOVAK, BALTIMORE, MD.—Dr. Smith's excellent presentation throws new light on several old problems, such as, for example, that of functional bleeding. Concerning the hormonal mechanism of the latter, the common assumption has been that the responsible factor is a prolonged and excessive estrogenic influence upon the endometrium, the periodic bleeding phases being due to drops in the level of these estrogenic principles. Dr. Smith's studies, however, indicate that we may have to consider not only this factor of hormone deprivation, but also, and perhaps more importantly, departures from the normal balance of the various chemical forms of estrogen. He emphasizes that the hormonal content of the urine represents merely the balance between hormone utilized and that which is destroyed, and that progesterone plays an important rôle in the regulation of this balance. The bearing of such studies upon our interpretations of urinary hormone assays is obvious.

In his discussion of both functional bleeding and pre-eclamptic toxemia, he referred to the possibility that estrogenic products might be the cause of the vascular changes associated with these conditions. I have long felt that there must be some such liaison between the hormonal factors concerned in functional bleeding and the vascular apparatus of the endometrium, especially the so-called spiral arterioles. After all, normal functional bleeding, like that of normal menstruation, is a primarily vascular phenomenon. The peculiar "blanching and blushing" phenomenon which Markee has described, and which is due to alternating phases of vasoconstriction, vasodilatation in these arterioles, is an essential part of normal menstruation, and it is certainly linked up with the normal factors of menstruation. Departures from the normal hormonal interplay must bring about abnormalities in this vascular response, and here one may expect to find the explanation of the local causes of functional bleeding. Concerning the latter there is still much uncertainty, some holding that the bleeding is due entirely to the occurrence of infarct-like necrobiotic areas, while others feel that in addition there must be an increased permeability of the blood vessel walls. Here lies a fertile field for studies of the sort which Dr. Smith has described today.

DR. GEORGE VAN S. SMITH, BROOKLINE, MASS. (closing).—It is quite obvious that all of this material is still in the realm of pure research. Our own enthusiasm for it is because it seems to shed a little light down a dark alley. That is, it gives us a lead toward the possible mechanism that results in menstrual bleeding and in pre-eclampsia, namely, a possible cause for the arteriolar spasm of these states.

it and any needed plastic work can be done at the same time. While there appears to be reason for believing that, if menstruation is stopped, the ovaries continue to function but a few years longer, these added years are usually sufficient to carry the woman to the time at which she would normally have had her menopause. The women treated in this way have been far more comfortable than those formerly treated by irradiation.

Fibroid Tumors.—In women in whom parturition has caused the uterus to be fairly movable, so that the cervix may be pulled down into the lower third of the vagina. We would exclude tumors too large to be easily delivered through the vaginal incision. We have in a few cases removed by morcellation tumors too large to be easily delivered, but we prefer in most cases to remove the larger tumors by abdominal section. Certainly morcellation is not an operation for the surgeon unskilled in this field. Intraligamentous tumors do not lend themselves to vaginal removal, and fibroids which have invaded the subvesical space are not good cases for vaginal operation. Fibroids associated with previous inflammatory disease which has left residues which diminish the mobility of the uterus and which may have left extensive adhesions, are best excluded from vaginal operation. We have done 30 operations for the removal of uteri containing fibroids.

Retrodisplacement.—In women in whom further childbearing is undesired or unwise, whose uteri are heavy and large, and in whom the uterus is fairly movable, this operation may serve a useful purpose. It is best reserved for the women who are in or near the menopausal years. It should not be done in the younger women. Often in these cases outlet relaxation demands attention and an unhealthy cervix is present. I believe that at least part of the relief which follows vaginal hysterectomy done for this condition is due to the fact that it disposes of the varicose veins of the broad ligament which so often accompany it. We have done 33 operations for this indication.

Prolapse and Descensus.—In cases in which the uterus protrudes partially or wholly from the introitus, we, in almost all cases, make use of vaginal hysterectomy. An occasional Manchester operation is done. Rarely, in a feeble old woman a LeFort operation is employed, and, occasionally, in women past childbearing or who are to be sterilized, and when the descensus does not cause the cervix to pass the introitus, we employ transposition of the uterus, with or without amputation of the cervix. Occasionally, in minor degrees of descensus, the bases of the broad ligaments are detached and fastened in front of the upper part of the cervix, often with amputation of part of the cervix. In all other cases vaginal hysterectomy is the procedure of choice. For extensive descensus or prolapse no form of abdominal suspension is used. We have done 97 vaginal hysterectomies for this indication.

Contraindications.—Our experience has impressed upon us that certain conditions make it unwise to adopt this method of approach. One of the most important of these is changes in intra-abdominal conditions produced by a previous operation. Adhesions of omentum or intestine

THE PLACE OF VAGINAL HYSTERECTOMY IN PRESENT-DAY GYNECOLOGY*

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(From the Department of Obstetrics and Gynecology of Northwestern University Medical School and of the Evanston Hospital)

DURING the past few years a number of papers have been presented to this Society upon the technic and indications of total and sub-total hysterectomy and upon the management of prolapse. As a sequence to these contributions I wish to discuss the indications and technic of vaginal hysterectomy. While I do not believe that all excisions of the uterus should be vaginal, I do believe that in many clinics a greater use might be made of this operation. Until five years ago this operation was done very rarely by us. This was because, in my earlier years, I became prejudiced against the operation. A few years ago my associates and I became convinced that a mode of treatment which was, in some cases, very valuable, was being neglected, and that, in order to give our patients the benefit of the method best fitted to their individual cases, we should make use of either the abdominal or vaginal route. Since that time we have done vaginal hysterectomies 266 times. During the same period 541 abdominal hysterectomies have been performed. This will evidence that we have not displayed the zeal of the convert in employing this procedure in all of our work. We believe, in the light of our experience up to this time that vaginal hysterectomy may be wisely employed in a number of groups of cases.

INDICATIONS

Functional bleeding	48
Prolapse	97
Fibroids	30
Retrodisplacement	33
Moderate descensus—outlet relaxation	55
Carcinoma of corpus	3
	<hr/> 266

Functional Bleeding.—We have done vaginal hysterectomy in 48 cases to control nonmalignant bleeding. Some years ago we gave up irradiation in these cases except in women in the later forties, as our experience showed that the discomforts of a menopause brought on some years sooner than it otherwise would have appeared were greater than those accompanying a surgical procedure. The removal of the uterus vaginally, unless the operation is otherwise contraindicated, affords a very satisfactory method of dealing with this condition. The cervix in many of these cases is in an unhealthy condition. The operation disposes of

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dominal operation is usually preferable. We have not considered vaginal hysterectomy as a means of managing carcinoma of the cervix as our usual means of treatment is irradiation.

Ovarian Tumors.—If hysterectomy is to be done upon a patient who also has an ovarian cyst, it is usually wiser to operate abdominally. We

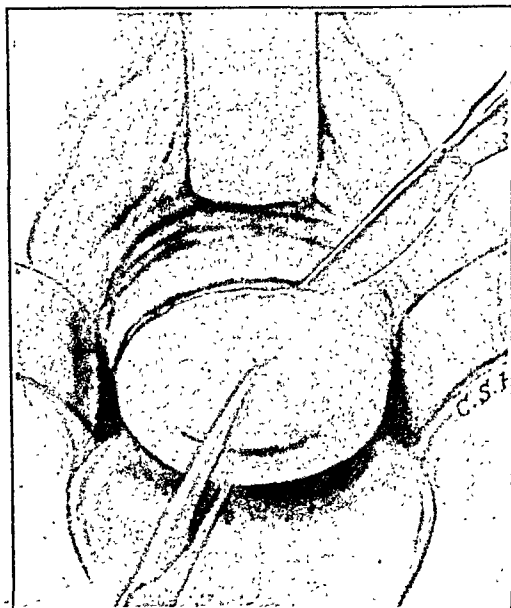


Fig. 1.

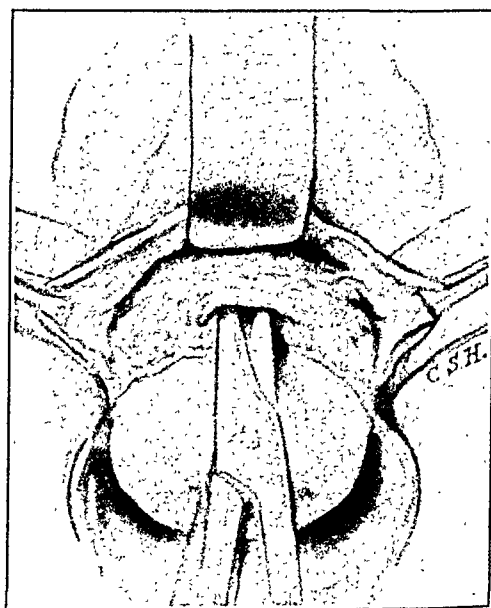


Fig. 2.

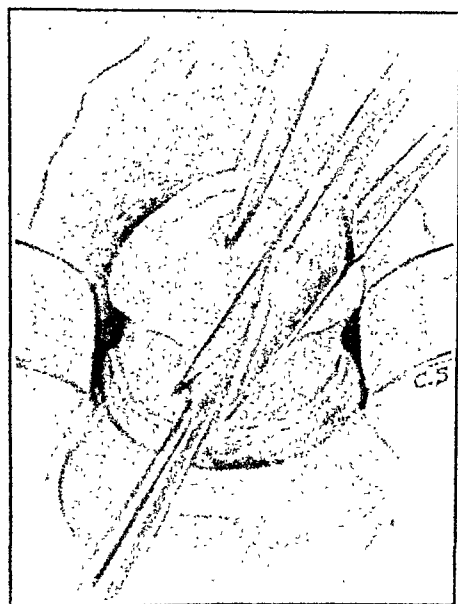


Fig. 3.

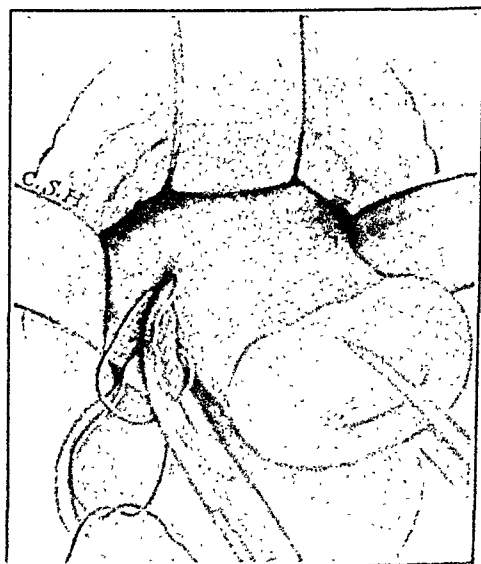


Fig. 4.

have, however, removed a number of cysts while doing vaginal hysterectomy. Cysts of moderate size and which are not adherent may often be removed easily. In one case unexpected adhesions were encountered, which rendered the operation more difficult, but did not prevent its completion without incident. Our present position is, that if hysterectomy

may cause the operation to be far more difficult and hazardous than it would otherwise be. Certain procedures, as retrodisplacement operations and ventral fixations, when the uterus has subsequently come down, cause vaginal excision to be particularly difficult. We have done a few such cases. The great majority of these should be attacked from above. Ventral fixation should be an obsolete procedure but upon two of the women upon whom we performed vaginal hysterectomy this operation had previously been done. In these two cases, although the uterus had later come down, the elongated band which connected the fundus uteri to the abdominal wall rendered it impossible to deliver the uterus either anteriorly or posteriorly. Pressure over the lower abdomen by the hand of an assistant aided materially in reaching the band at the fundus which it was necessary to divide. It is usually wiser to deal with these cases otherwise than vaginally. When doubt is felt as to the practicability of the vaginal operation because of adhesions, a posterior colpotomy may be done. If the uterus is of normal, or nearly normal, size, its surface may be palpated and information obtained as to the presence or absence of adhesions. The operation may continue vaginally or the colpotomy would be closed and the uterus removed abdominally after completing any needed plastic work. In general, if doubt is felt, it is best to operate abdominally.

It is better not to attempt to remove the uterus vaginally if there has been a preceding pelvic inflammation sufficiently severe to cause adhesions of bowel or omentum in the pelvis. A deft and experienced operator may deal with these cases but it is usually better to attack them from above.

We have, in a few cases, removed by morcellation, fibroid tumors which were too large to be delivered vaginally. This is a procedure which may be carried out by one who has developed a considerable skill with this operation but should not be attempted by others. It is very useful, if one has misjudged the size of a tumor, for it may be removed by morcellation with far less trauma to the patient than would be caused by forcefully delivering a large mass through an opening of insufficient size. We use it only occasionally.

In many cases of carcinoma of the corpus uteri the size and mobility of the uterus would render vaginal removal possible. In addition, many women with cancer of the uterine body have more or less outlet relaxation which would facilitate the operation still more. We do not believe, however, that vaginal removal is wise and have done it in only 3 cases. In performing abdominal hysterectomy for corporeal cancer, our first move is to place straight clamps close to the uterus on either side to prevent carcinoma cells from being pushed into the parametrium through the lymphatics and blood vessels by unavoidable manipulation of the uterus. The upper part of the broad ligaments cannot be blocked off if the operation is being done vaginally until a late stage of the operation. If there were also a marked descensus, this disadvantage might be less. The tenaculum in delivering the uterus is a disadvantage as it should be traumatized as little as possible. In these cases the ab-

the anterior portion of the repair in this case remaining intact. In one other case a complete failure occurred necessitating later operation.

The uterosacral ligaments, after being transversely united, must be attached to the posterior margin of the united broad ligaments in order completely to close the posterior portion. The anterior edges of the united broad ligaments are attached on either side of the urethra underneath the rami of the pubes in order to retain the bladder. Incontinence of urine may be dealt with as the operation proceeds, and, if fascial flaps are available in the anterior wall, they are dissected free and united. A perineal plastic completes the operation. A small rubber or gutta-percha drain is usually used at the mid-point of the suture line in the vault.

For the cases in which a marked descensus is not present, it is not necessary to open the anterior vaginal wall unless incontinence, cystocele, or urethrocele is present for which plastic work is needed. A simple incision at the lower limit of the bladder is made. The bladder is freed from the anterior uterine wall by scissors dis-

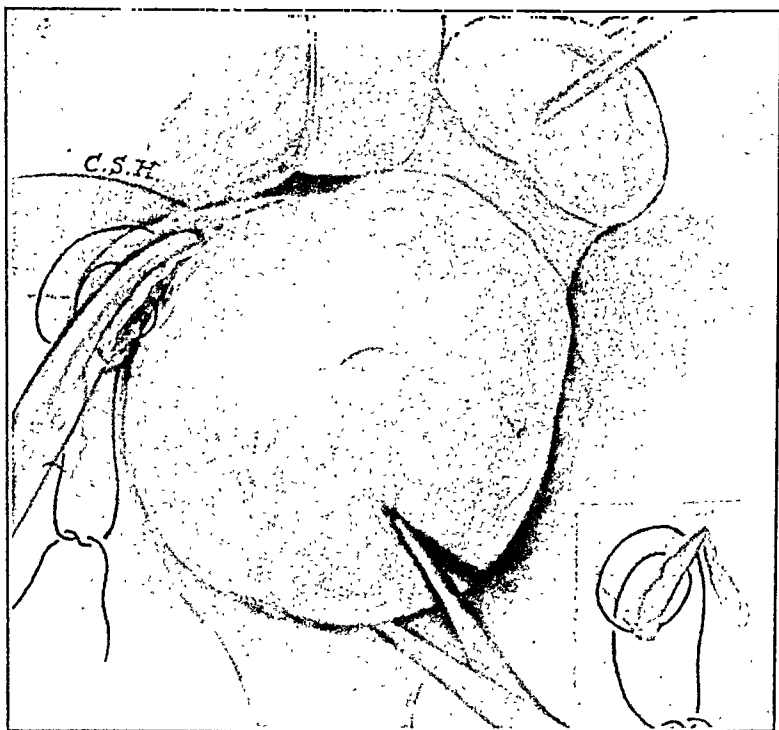


FIG. 7.

section and pushed upward. The anterior peritoneum is opened, or, if it is not easily identified, it is left until later. The incision is extended around posteriorly and the posterior peritoneal pouch opened. The uterosacral ligaments are caught on either side with clamps, cut and the clamps replaced by suture ligatures. It is better to replace all clamps at once by suture ligatures for two reasons. First, a clamp allowed to remain may slip and cause bleeding, and, second, the removal of clamps at once gives more space and greatly facilitates later work. As the uterosacral ligaments and the bases of the broad ligaments are divided the uterus may be brought lower, and, if the anterior peritoneum has not been opened, it may now be done easily. When sufficient of the uterine supports have been divided the corpus is delivered. We have found the delivery of the uterus through the posterior vault, instead of anteriorly as is usually suggested, a very satisfactory measure. This was suggested to me by Heaney, but I have since learned that it was done forty years ago by Joseph Price. It is easier and usually requires less force than delivery anteriorly. Two clamps are placed on either side, and the uterus is removed.

tomy is to be done and an ovarian cyst is present, unless the cyst is freely movable and of such a size that it may be removed with reasonable ease, and unless the operator feels at home in the vaginal field, abdominal section is preferable. Should either a dermoid or a malignant cyst be suspected vaginal approach should not be considered. Unless the cyst is small it must be punctured before removal, which is unsafe in either of these. In some European clinics vaginal removal is practiced even though the cyst be large. We prefer a more conservative attitude.

In stating a number of quite definite contraindications, we indicate clearly that we do not feel that this procedure should be used in all cases. We believe that the gynecologic surgeon should be master of both

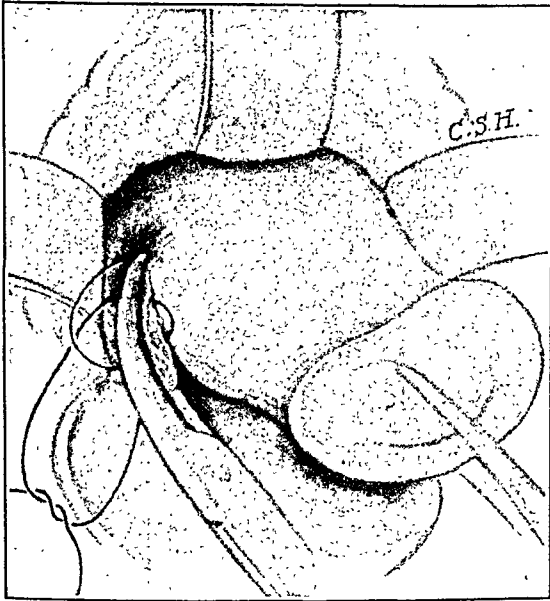


Fig. 5.

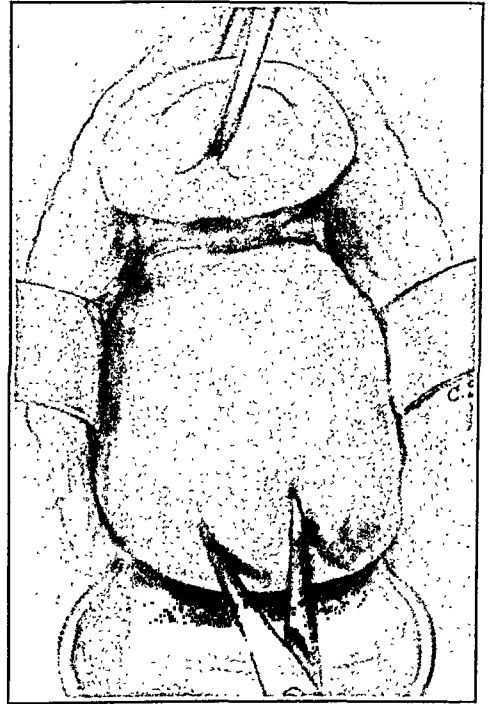


Fig. 6.

methods, and that his choice of the procedure to be used in a given case should be based wholly upon the conditions found in that case and not influenced by a preference for one or a feeling of inability to use the other.

TECHNIC

After trying various ways of doing the operation we have settled fairly well upon two procedures. For the marked descensus with the uterus protruding partly or wholly from the vagina the procedure sometimes called the Mayo operation, but which was probably first done by J. Riddle Goffe, has been very satisfactory. The technique of this operation has been well described and illustrated by George Gray Ward. It is of the greatest importance that the uterosacral ligaments be united by transverse sutures and in some cases in which the descensus is extreme, that the pouch of Douglas should be dissected out. This removes the hernial sac through which the accompanying enterocele descended and closes the hernial opening. Failure to attend to this essential point of technic may cause a later protrusion at the posterior vault. Failure to appreciate this fact caused one recurrent enterocele.

has been far smoother than would be expected in a group of similar age upon whom a combined vaginal and abdominal operation had been done. The fact that in the cases of marked descensus or prolapse the operation is almost extraperitoneal doubtless contributes a great deal to the smoothness of the recovery.

COMPLICATIONS AND MORTALITY

Cystitis and pyelitis	6	2.26%
Postoperative bleeding	4	1.5 %
Phlebitis	2	0.75%
Pelvic abscess	1	
Total morbidity	9.02%	
(American College of Surgeons Standard)		
Mortality	0	

In this group we had a morbidity rate of 9.02 per cent, using the American College of Surgeons standard, that is, a rise to 100.4 per cent on any two days excluding the day of operation. An attempt to extend the applicability of the vaginal route greatly beyond the limitations already stated would almost certainly be followed by an increased mortality and morbidity. This would certainly be so in the hands of operators not thoroughly at home in the vaginal field.

An objection which is sometimes made is that the vaginal operation shortens the vagina. This we find to be true in many of the patients operated upon for prolapse. The shortening is not extreme and in many of these older patients is of little importance. In the women operated upon for indications other than prolapse, in whom the technic shown in the illustrations is used, there is no shortening.

OPERATIVE COMPLICATIONS

In two cases an injury of the bladder occurred. Both were recognized at once, the wound closed, and recovery was uninterrupted. In one case active bleeding from the uterine artery occurred due to the slipping of a clamp. This was controlled before serious loss of blood. There were 4 cases of postoperative bleeding. In one of these the bleeding had nothing to do with the hysterectomy but came from the perineum, upon which a plastic operation had been done. In the 3 others it came from the region of the uterosacral ligaments and was controlled by placing a six inch clamp, which was left for thirty-six hours upon the bleeding area. Closer attention to this area in closing the operative wound has prevented further bleeding.

In one case a serious thrombophlebitis followed operation. Recovery followed conservative management. In one case a pelvic abscess developed six weeks after operation. This was opened and recovery followed. In two patients who were operated upon for prolapse unsatisfactory results followed. In one case the anterior portion of the reconstruction was satisfactory but an enterocele followed. This was an early case in which the patient was operated upon before we had come to appreciate the importance of careful closure of the posterior peritoneal pouch and the approximation of the uterosacral ligaments.

In closing the wound, it is best to attach the stumps of the broad and round ligaments and the uterosacral ligaments to the vaginal angles. This is done by passing a suture through the anterior vaginal wall and peritoneum, through the stumps of the broad, round, and uterosacral ligaments, and lastly through the posterior peritoneum and vaginal wall. This supplies support for the vaginal wall and also brings together the peritoneum of the anterior and posterior leaves of the broad ligaments and of the pelvis, thus leaving a good peritoneal covering. Closure is completed by interrupted sutures between these two. Occasionally a suture outside one or both of the two first sutures is needed to bring the vaginal wall together completely. Drainage is needed only exceptionally. The most annoying bleeding is usually from the cut edge of the posterior vaginal wall. A temporary suture is sometimes used to control this. This mode of closure approximates the vaginal walls so that the anterior and posterior walls lie smoothly in contact. Approximation of the wound in the vault by an anteroposterior suture line disturbs the normal relationship of the anterior and posterior walls and also may, as the lateral vaginal structures are drawn inward, tend to displace or kink the ureter. A transverse suture line is preferable.

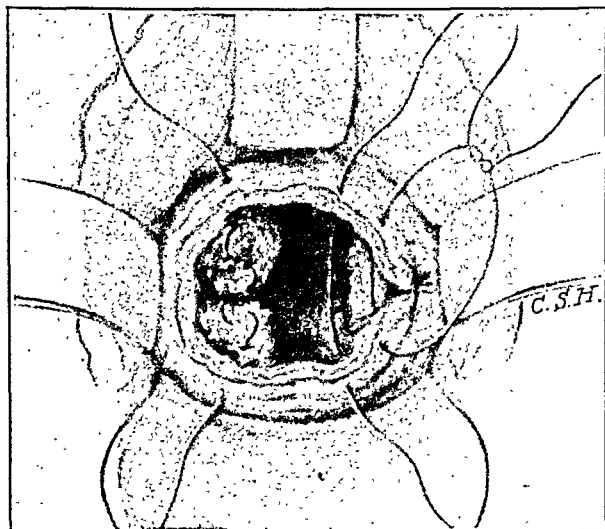


Fig. 8.

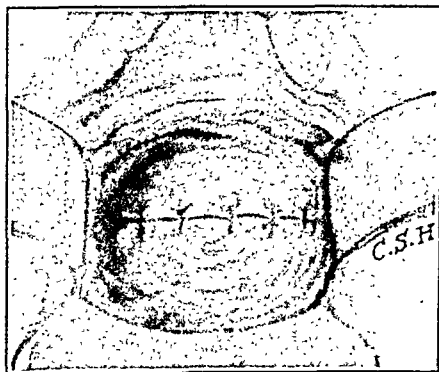


Fig. 9.

RESULTS

In this series of 266 cases there were no deaths. This statement does not mean that the operation is without mortality and we freely admit, while every care has been used, that good fortune has also played a part and we do not expect to operate indefinitely without mortality. During the time covered by this report, 451 subtotal hysterectomies were done. In this same period 90 total hysterectomies were done. The freedom from symptoms referable to the cervix in our vaginal cases has caused a greater use of the total operation during the latter part of this time. Of the total number of hysterectomies 31.5 per cent were done vaginally.

The postoperative course of these cases has been smoother, on the average, than a similar number of abdominal hysterectomies. The advantage of vaginal attack is most apparent in older women, particularly those operated upon for marked descensus. While the morbidity was a little greater in this group than in those operated upon by the simple technic used in operations done for other indications, recovery

When the cul-de-sac is opened I think it worth while tipping the table and putting the patient in a partial Trendelenburg position. Occasionally the patient strains and exerts a little intra-abdominal pressure so that loops of bowel may present at the vaginal vault. It is simpler to tip the table at that stage of the operation than to pack bowel away.

I like the transverse closure of the vault. Ordinarily I do not unite the uterosacra in the midline. I do, however, when they are unusually long, or when there is enterocele.

Our morbidity is more than double that shown by Dr. Danforth. We had one fatality in a private patient of my own which I think it proper to report at this time. After an ordinary uneventful hysterectomy she developed fever and on the fourth day we instituted sulfanilamide therapy in rather considerable doses. The patient developed an intense rash with urticaria, which went on from pink to purple in color, and in the week following, in spite of every measure that we could institute, the termination was fatal.

DR. LILIAN K. P. FARRAR, NEW YORK, N. Y.—Dr. Danforth has called attention to other conditions than prolapse that might be operated upon by the vaginal route. I am glad to learn that he prefers to do a vaginal hysterectomy rather than apply radium in functional bleeding in women at the time of menopause. By vaginal hysterectomy the cervix does not remain a menace for the rest of a woman's life, as after irradiation of the fundus, and a more comfortable menopause is secured for the patient if the ovaries are left at operation and not destroyed by irradiation. By restricting the vaginal operation to uteri and to ovarian neoplasms that are not so large but that one can be sure of their easy delivery through the pelvis, to retroversion or to chronic adnexa if not adherent, one may do vaginal hysterectomy and all needed plastic work in less time than a combined vaginal and abdominal operation, and with less shock. I believe though that a known or even suspected carcinoma of the fundus should be done by the abdominal route with clamps applied to the sides of the uterus as Dr. Danforth does.

There are several points in technic that I would like to speak of and the first is the closure of the wound anteriorly. Dr. Danforth says, "The anterior edges of the united broad ligaments are attached on either side of the urethra underneath the rami of the pubes in order to retain the bladder." This is never necessary in total abdominal hysterectomy, why is it necessary in vaginal hysterectomy? It causes distortion of the upper pelvic floor, displacement of the ureters and may produce an enterocele.

The bladder was in its normal position resting upon the uteropubic fascial plane, with a split in the fascia which was the beginning of a cystocele. Dr. Danforth says, "If fascial flaps are available in the anterior wall they are dissected free and united." I have never seen a case where these flaps could not be dissected free and when sutured together the constructed fascial plane may then be sutured by its posterior edges transversely to the broad ligaments exactly as we do in total abdominal hysterectomy and restore the bladder to its normal position in the pelvis.

The final point is the repair of an enterocele. This condition has long been of interest to me since I saw the monumental work of Tandler and Halban ("The Anatomie und Aetiologie der Genital Prolapse"). I believe that to repair an enterocele correctly one must dissect it out and suture the uterosacral ligaments together.

PROFESSOR LUDWIG ADLER.—Dr. Danforth's mortality record has been excellent and I must confess that we have not been as fortunate as he has been. This may in part be due to the fact that our indications are somewhat different from Dr. Danforth's. A great number of his cases were of prolapse or of descent. We have used for such cases either the interposition operation or a procedure similar to that of Pothergill, or in old women the Le Fort operation. Following hysterectomy for prolapse we have seen quite a number of recurrences in the form of hernia of the vagina, and therefore, prolapse in our country is rarely considered an in-

Our present opinion is, that vaginal hysterectomy is a procedure of great value and that it is worthy of more extended use than it receives in many clinics today. Strongly to advocate its adoption by occasional operators, or by the general surgeon without gynecologic training would probably not be to the advantage of the patients of these men. While a clever general surgeon may learn the technic of this as of other operations, in the hands of most of the individuals who make up these groups, morbidity and mortality would be too high. It is a procedure for the gynecologically trained surgeon. It is more difficult, in some cases much more difficult, than the average abdominal hysterectomy.

In cases to which the operation is well adapted, convalescence is, on the average, smoother than in abdominal cases. Mortality should, in expert hands, be essentially the same in uncomplicated total abdominal hysterectomy and vaginal hysterectomy. A painstaking vaginal toilet is an essential part of either operation.

Although I ascribe a high value to the operation I think that its application should be kept within logical limits. If used in cases such as those discussed under the head of contraindications, the dangers of the operation increase. A careful evaluation of the anatomic and pathologic characters of each case is essential, and the choice of the route of operation must be based upon a consideration of these.

DISCUSSION

DR. JOSEPH L. BAER, CHICAGO, ILL.—When we decide that we are going to try out an operation, we try within reasonable limits to make the patients fit that operation until we have had one, two, or three years of experience with that operation. That is entirely justifiable in the hands of men who are careful of the ultimate welfare of their patients. We did this in our prolapse series when we worked first with the interposition operation, then vaginal hysterectomy, and now parametrial fixation.

Nevertheless we sometimes give way to departmental reactions. For instance, vaginal hysterectomy gives way to total hysterectomy when the supports of the uterus are good, or when the cervix does not come down reasonably well. The vaginal approach is indicated when the cervix is bad and the uterus is mobile, and especially when a plastic operation anteriorly or posteriorly, or both, is necessary. I like parametrial fixation particularly in those instances of greater degrees of prolapse than those which Dr. Danforth prefers. Partial protrusion of the uterus is usually protrusion of the cervix, and I see no reason for not utilizing parametrial fixation for that type of prolapse instead of vaginal hysterectomy. We likewise use the Le Fort operation more than do Dr. Danforth and his group. I like it for the elderly woman with the atrophic uterus.

The essentials of technic in vaginal hysterectomy are these: First, during the closure of the opening which we have created at the top of the vagina, we must anchor the vaginal vault one way or another. Second, when the bladder has prolapsed, bladder and urethra must be elevated and the supports properly reconstructed. Third, when there is a deep cul-de-sac, that must be completely repaired. We do not drain either in the ordinary types or in the prolapsed types of vaginal hysterectomy. There should be no necessity for drainage in the vaginal vault nor packing of the vagina.

In the actual technic my associate, Dr. Reis, is trying to convert me to the amputation of an unduly long cervix after it has been completely separated and before rotating the uterus on its transverse axis. In that way the uterus is almost ball-like and can be rotated equally freely anteriorly or posteriorly.

HYPERTENSION AND PREGNANCY*

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WE HAVE analyzed the records of over 1,200 toxemic patients, treated by us during a six-year period, to determine the importance of hypertension in pregnancy and the practical value of a new classification of the toxemias. It has been our belief for some time that hypertensive arterial disease is the primary condition in many of the so-called "toxemias of pregnancy," and that the edema and albuminuria which may occur in this type of toxemia are secondary to the vascular condition. Other investigators have assigned as much importance to the presence of edema or proteinuria as to the hypertension. Such an assumption presupposes some type of kidney lesion to explain the albuminuria and either a renal lesion or an abnormal tissue physiology to account for the edema. This difference in the interpretation of the significance of these signs is largely responsible for the somewhat chaotic condition of the classification of the toxemias of pregnancy.

Prior to 1926, patients with toxemia of pregnancy were divided into eclampsia, pre-eclampsia, and nephritic toxemia or chronic nephritis. The latter condition was likely to recur in subsequent pregnancies, and usually between pregnancies there was a hypertension and often an accompanying proteinuria.

Stieglitz in 1926 stressed the importance of hypertension in pregnancy and divided the toxemic conditions into: (1) those due to the pregnancy, eclampsia, and pre-eclampsia; (2) those due to a pre-existing vascular and/or renal disease; and (3) those due to thyrotoxicosis and acute nephritis.

The same year Stander and Peckham published their report which grouped patients with toxemia into eclampsia, pre-eclampsia, chronic nephritis, and low reserve kidney. The latter condition was distinguished by a moderate hypertension, a small amount of albumin in the urine and slight edema. These abnormal findings had disappeared by the end of the puerperium, and, although the condition returned with each pregnancy, there was no increase in the severity of the signs and no demonstrable damage to kidney, heart, or vascular system. Since their original paper, Stander and Peckham in separate reports have admitted that the diagnosis of low reserve kidney has often been incorrect. Finally, Stander in 1938 stated that the low reserve kidney might be a mild form of pre-eclampsia. He also stated that the term "chronic nephritis" as used by him implied kidney damage due either to a previous acute glomerulonephritis or to a nephrosclerosis.

Herriek and Corwin in their first report, in 1927, stressed the importance of hypertensive arterial disease complicated by pregnancy. Eclampsia and chronic nephritis were additional groups.

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dication to perform a vaginal hysterectomy. On the other hand, we do vaginal hysterectomy as a method of choice in fibroids if the tumor is movable even if the uterus is double the size of a fist.

For the treatment of bleeding in a uterus which has no fibroids, I personally have been using intrauterine radium treatment, but with so small a dosage that the troubles of menopause do not occur. It seems to me that this treatment is less dangerous than the complications which sometimes follow vaginal hysterectomy.

As to the technic I usually bring out the uterus from the anterior plica. In some cases the procedure of bringing it out from the pouch of Douglas is advisable. If the uterus is not easily movable or if the uterus is large, amputation of the cervix is useful. If there is difficulty in bringing out the uterus, as in inflammatory cases, or when large fibroids are present, we split the whole uterus or perform a morcellement. One point which seems very important to me is that all the stumps should be placed extraperitoneally. Furthermore, if we remove the adnexa, we take care that the corner suture of the peritoneum catches the infundibulopelvic ligaments. We do this for two reasons: first, to prevent adhesions, and second, because if there is hemorrhage from one of the vessels it can be controlled without opening the peritoneum. After closing the peritoneum I always tie the stumps to the corner of the vagina so that there is a retraction of the vagina which prevents later descent.

We do perform the vaginal operation as a routine operation for cancer of the body if the uterus is not too large.

May I add that personally within the last twenty years I have done nearly all of my vaginal operations, including uterine cancer, under twilight sleep and local anesthesia. It has not only the effect of lessening the shock of operation, but the bleeding is less and the dissection of tissues becomes very easy.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—Since using ethylene gas for anesthesia I have done 831 vaginal hysterectomies in nonmalignant disease with 3 fatalities as previously reported. Most of the operations were done for fibroids. Among these cases were 197 nulliparous patients. Some of these were with intact hymens so that the hymen had to be incised in order to enter the vagina. In the last 369 vaginal hysterectomies, it was necessary to morcellate 93 times. In this list I have not included cases of carcinoma of the body of the uterus which I prefer to operate upon rather than to irradiate. Whenever possible I operate upon these cases vaginally, because they are for the most part elderly women and will stand a vaginal operation much better than an abdominal one. There has been no mortality in these cases of cancer of the body of the uterus.

For a considerable length of time now I have been operating upon the cases of carcinoma of the cervix after they have been treated with radium and have healed, hoping in this way to increase the number of ultimate cures. I do either a Schauta or a Wertheim on these cases, depending upon the conditions.

DR. DANFORTH (closing).—Recently we have been doing two-thirds of our hysterectomies by the abdominal route and only one-third from below. The choice of procedure is an individual matter. One who has developed a great deal of skill can take out almost any uterus vaginally if he chooses to do it. Whether it is wise to do so from the standpoint of the patient's safety is another thing and I think one should choose the operation which is safer for the patient and that causes certain limitations.

Transverse closure has a definite advantage in that it does not drag in the walls of the vagina and is rather less likely to produce kinking of the ureter.

Dr. Adler's point about bringing the stumps of the ligaments into the vaginal angle is very important. We find it useful except when we are dealing with prolapse.

As our skill increases with an operation we are inclined to use it more and more. We find ourselves sometimes getting a little more liberal in the use of the operation, but I think this should not be done until one increases one's skill.

development during pregnancy and their persistence longer than six weeks post partum. The renal function is in the lower limits of normal or it may be below normal. Ophthalmoscopic examination usually shows more marked retinal vessel changes than in the essential hypertension group. Subsequent pregnancies almost invariably intensify the various symptoms and signs. The condition may be the result of a long-standing essential hypertension, pyelonephritis, or chronic glomerulonephritis. The only difference between Groups B and C is one of duration and the amount of vascular and renal pathology. It seems to us that the subdivision of the patients with hypertension into Groups B and C permits a more logical separation of pregnant patients with increased blood pressure, because it will be noticed subsequently that the patients classified as having essential hypertension have many characteristics which distinguish them from the vascular-renal disease group and also from those having pre-eclampsia.

We have divided each group into mild and severe according to the following criteria: A severe case is one in which (a) two or more of the following signs are present: the systolic blood pressure is over 170, proteinuria is over 0.3 per cent or 3+, or there is marked edema of the legs; (b) at least one of the following signs is present: systolic blood pressure is over 200, proteinuria is over 0.5 per cent or the urine solidifies on testing, or there is a generalized edema; (c) the occurrence of one of the signs listed in (a) and the development of marked cerebral, visual, gastrointestinal, or renal symptoms. All other toxemic patients are classified as mild. It is obvious that the amount of protein in the urine and the degree of edema are dependent on personal observation. For the past two years we have been determining the twenty-four-hour excretion of albumin which is a better guide than the daily testing of one specimen. Our only quantitative method for measuring edema is to determine the weight gain during pregnancy. However, with these relatively crude qualitative measurements, we are able to demonstrate marked differences between the mild and severe conditions and between pre-eclampsia, vascular-renal disease, and essential hypertension.

Undoubtedly, mistakes have occurred in classifying and in evaluating the severity of signs and symptoms, but we have not deleted any cases because the diagnosis or degree of severity was questionable. The majority of the patients were seen by us and a tentative diagnosis as to the kind of toxemia and degree of severity was made on discharge from the hospital. However, this report is based on records which were only considered complete at six months or longer after delivery. These charts were classified during the winter of 1937 and again in 1938. Comparatively few diagnoses were changed, but the degree of severity was frequently altered from severe to mild. It seems that as time passes one forgets how sick the patient actually was with the result that the clinical condition has undoubtedly been underestimated in many instances.

Fig. 1 illustrates the effect of age, parity, and surface area. The latter was used because it is a function of the height and weight of the patient. Seventy-four per cent of the pre-eclamptic patients are under 30 years of age, as compared with the vascular-renal group in which only 34 per cent are under 30. Sixty-six per cent of the pre-eclamptic patients are in their first pregnancy, while only 11 per cent of the vascular-renal

Patients with toxemia of pregnancy at the Boston Lying-in Hospital since 1936 have been divided into the following groups:

A. There is evidence of disease independent of pregnancy: (a) Nephropathies associated with arterial vascular disease, (b) inflammatory nephropathies, (c) degenerative nephropathies.

B. There is no evidence of disease independent of pregnancy: (a) Pre-eclampsia Grade 1, (b) pre-eclampsia Grade 2, (c) eclampsia. Our only objection to this classification is the use of the word nephropathy which implies that there is renal pathology or impairment. No one, so far as we know, has been able to demonstrate any impairment of kidney function or alteration in the urinary sediment in patients with an early essential hypertension.

Formerly we grouped our patients into eclampsia, pre-eclampsia, chronic nephritis, acute glomerulonephritis, and nephrosis, but since 1933 we have restricted the term chronic nephritis to those patients who have had a previous acute glomerulonephritis. Those patients whom we formerly classified as having chronic nephritis are now placed either in a vascular-renal disease or essential hypertension group.

Pregnancy does occur in patients with essential hypertension and vascular-renal disease and since these terms are commonly used by the internist it would seem logical for us to apply them where indicated instead of using vague or possibly misleading terms, such as nephritic toxemia, recurrent or latent nephritis, low reserve kidney, etc. The opinion which some internists have of the obstetrician's knowledge of vascular-renal disease is indicated by the following quotation: "Again the fact must be faced that ignorance of these diseases [toxemias of pregnancy] is abysmal," which appeared in a recent article on hypertension by Page. Furthermore, if such a classification with the addition of the terms pre-eclampsia and eclampsia would meet all requirements for distinguishing the various toxemias of pregnancy, further studies of these conditions would be simplified and there would be less conflict of opinion with the internist. This classification is not original with us but has been used by other investigators in various forms.

Our patients are grouped as follows:

A. Pre-eclampsia.—The appearance in a normal pregnant woman and/or disappearance by six weeks post partum of one or more (or all) of the following: (1) A systolic blood pressure of 140 or more for two days or longer. (2) An edema of at least the ankles and legs which has no obvious etiology. (3) A proteinuria which is present for two days or more (a clean specimen and no urinary tract infection). (4) Cerebral, visual, gastrointestinal, and renal symptoms may also occur.

B. Essential Hypertension.—A systolic blood pressure of 140 or more for two days or longer which is either present before pregnancy or appears during pregnancy, and persists longer than six weeks post partum. As term is approached there may be slight edema and proteinuria. The height of the blood pressure is there may be slight edema and proteinuria. The height of the blood pressure is usually out of proportion to the degree of edema and albuminuria. The renal function is within high normal limits. The ophthalmoscopic examination reveals either a normal retina or at the most only a slight narrowing of the retinal vessels. Occasionally the blood pressure is within normal limits between pregnancies, but it is always very labile, in that the response to various stimuli is abnormal.

C. Vascular-Renal Disease.—This disease is characterized by the presence of any two or more of the following signs: Hypertension, edema, or proteinuria before or

do not believe that repeated pregnancies cause the disease, but that they do aggravate and accelerate the disease process. Furthermore, repeated pregnancies usually signify increasing age and many of these women, even if they had had no children, would unquestionably have ultimately developed vascular-renal disease. The hypertension group is intermediate, but the number of older women, of multiparas, and of overweight women is apparent.

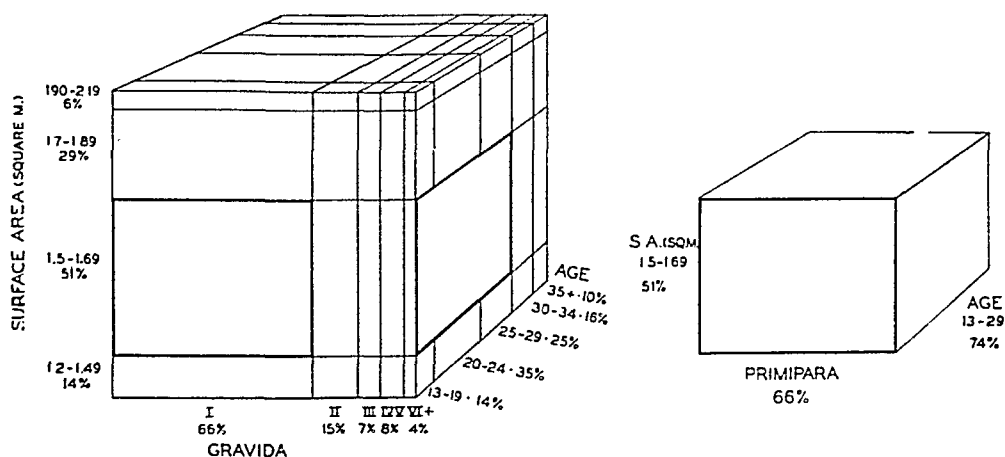
The amount of protein in the urine with but few exceptions was determined qualitatively, and as a result there is no correlation with any of the other measurements or signs. Harden, Barker, and other investigators have emphasized the importance of a nitrogen balance in patients with albuminuria, or as Harden termed it, "protein stabilization." However, except in a few patients who had a nephrosis we have not been concerned about the protein loss, because it usually amounts to less than 3 gm. and rarely exceeds 5 gm. per twenty-four hours. We urge that instead of testing a daily specimen, the twenty-four-hour excretion of protein be determined for its diagnostic and prognostic value. Thus we hospitalize the patient when the proteinuria amounts to 5 gm. or more per twenty-four hours, and if this amount persists for several weeks, we know that a high percentage of the fetuses will die in utero because of massive placental infarction, retroplacental hematoma, or abruptio placentae. Excretion of these large amounts of protein usually occurs in the vascular-renal group. The pre-eclamptic patient may excrete as much as 4 per cent protein in the urine, but this concentration is reached only when the urine is very concentrated and the total amount of albumin lost amounts to 1 or 2 gm. The patient with essential hypertension rarely excretes much albumin. The ambulatory patient can save all urine for a twenty-four-hour period, measure it, and bring a sample of the mixed twenty-four-hour volume for protein and chloride analyses. The latter determination will aid in determining whether or not the patient is adhering to a salt-poor or salt-free diet.

The average gain in weight during normal pregnancy, based on published reports and our own data, is 9.4 kilograms. Forty-three per cent of the pre-eclamptic group, 25 per cent of the vascular-renal, and 21 per cent of the hypertension group gained over 10 kilos. Twenty-nine per cent of the pre-eclamptic, 14 per cent of the vascular-renal, and 13 per cent of the hypertension group gained over 12 kilos. The average gain per week of normal pregnant women while under observation amounts to 0.45 ± 0.17 kilos. Seventy-four per cent of the severe pre-eclamptic, 49 per cent of the severe vascular-renal, and 23 per cent of the severe hypertension group gained at a rate greater than 0.6 kilos per week. Thus not only is it important to weigh the patient, but the average gain per week should always be calculated, because quite often it is the first sign of impending toxemia.

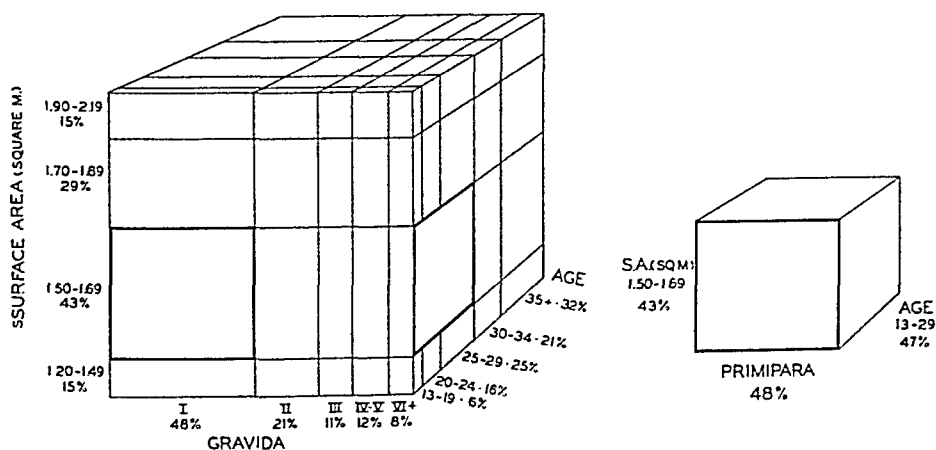
The relations between the weight gain per week, systolic blood pressure and presence or absence of edema in the severe groups are depicted in

group are primiparas. Thirty-five per cent of the pre-eclamptic group, in contrast with 52 per cent of the vascular-renal group, have a surface area greater than 1.7 sq. m. It is obvious that the multipara of 30 years or more and overweight, who develops evidence of toxemia in pregnancy, is more likely to have vascular-renal disease than pre-eclampsia. We

PREECLAMPSIA



ESSENTIAL HYPERTENSION



VASCULAR-RENAL DISEASE

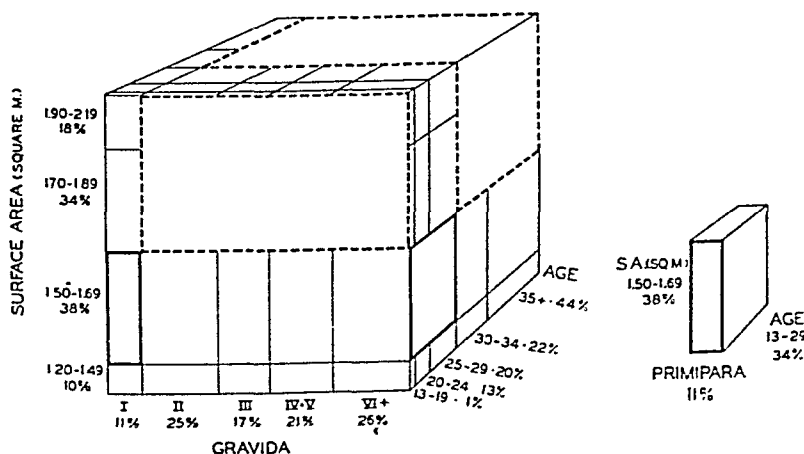


Fig. 1.—Characteristics of modal group as to age, parity, and surface area for pre-eclampsia and comparison with essential hypertension and vascular-renal groups.

bined in the figure as ++. It is obvious that the majority of the pre-eclamptic patients have a systolic blood pressure under 180, abnormal gain in weight per week, and a marked edema. The majority of the vascular-renal and hypertension groups have a systolic blood pressure which is over 180. Eighty-six per cent of the hypertension group, 73 per cent of the vascular-renal group, but only 34 per cent of the pre-eclamptic group had no or only + edema. No patients with essential hypertension had marked edema and none gained more than 0.8 kilos per week. It is evident that this group differs from the pre-eclamptic in that the majority of the patients have a much higher blood pressure, comparatively few have edema, and the weight gain is within normal limits.

The hypertension of pre-eclampsia differs from that of the other two groups in several ways. First, there is a difference in degree. Second, patients with pre-eclampsia give little or no increase in blood pressure to the "cold test" but do give a marked response to the injection of pituitrin. Patients of the other two groups usually give a marked response to the "cold test" and none to pituitrin. There has also been the report by Allen and Adson of a patient who had had a sympathectomy for an essential hypertension, subsequently became pregnant and again developed a hypertension which subsided when the pregnancy was terminated. This phenomenon seems to indicate that the hypertension associated with pre-eclampsia is humoral rather than nervous in origin.

The diastolic pressure shows marked variations but on the whole the systolic is a more sensitive indicator of approaching toxemia. Simon made a similar observation, stating that in one-fourth of his patients with toxemia the increase of the systolic blood pressure antedates the appearance of proteinuria or edema by from one to twelve weeks.

We have had six patients with an essential hypertension in whom the blood pressure was lower during pregnancy than it was either ante partum or post partum. It must be remembered that the hypertension is merely a sign of an abnormal cardiovascular-renal system and that the same disease is present with a blood pressure of 160/90 as with one of 210/140. Therefore, the hypertension is just as significant in the patient with the low blood pressure as in the one with the high. As a matter of fact, it is even more important because the duration of the disease has usually been shorter. Consequently adequate treatment may give a greater life expectancy than in the case of the patient with the very high blood pressure.

We have also had two families, in each of which two sisters had an essential hypertension which apparently had its onset in pregnancy. Unfortunately, there were no records of the blood pressure before the pregnancy. This familial tendency to hypertension is well known, but the onset in two sisters in pregnancy is rare and should be investigated further, especially in identical twins.

The appearance of the characteristic cerebral, visual, gastrointestinal, and renal symptoms in a toxemic patient always suggests that con-

Fig. 2. The average of the maximum blood pressures over a twenty-four-hour period was calculated and this figure forms the basis for our tables. Edema was described as follows: + means a definite pitting on pressure of the tissues over the lower third of the tibia; ++ means marked pitting over the entire tibia; +++ means that there is an associated edema of hands and face; ++++ means anasarca. Grades ++ and +++ are com-

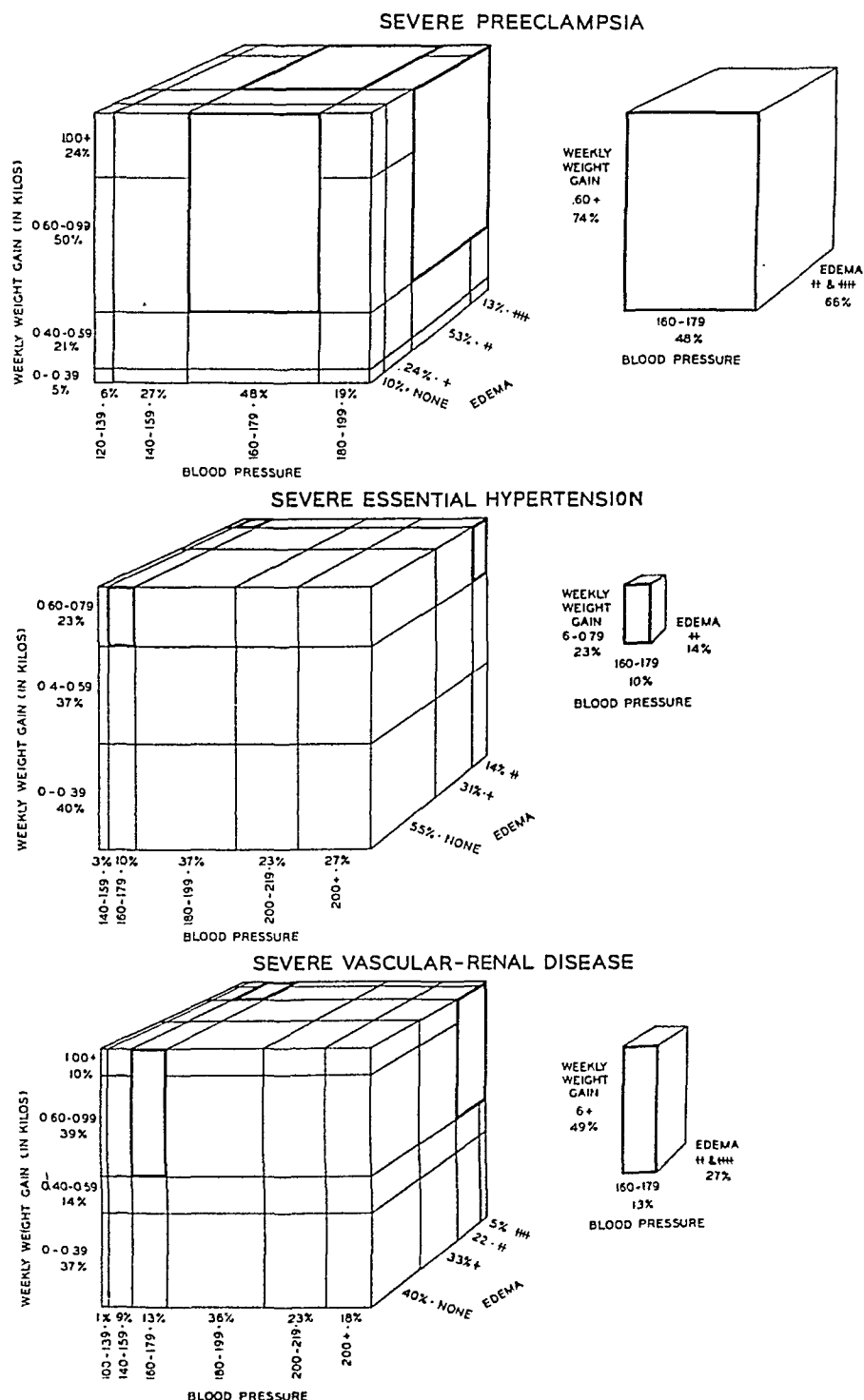


Fig. 2.—Characteristics of modal group as to weekly gain in weight, systolic blood pressure, and presence or absence of edema for severe pre-eclampsia and comparison with essential hypertension and vascular-renal groups.

nosis. Abnormal changes in the vessels of the retina were described in 35 per cent of the mild pre-eclampsies, 51 per cent of the mild vascular-renal group, and 5 per cent of the mild essential hypertension group. More extensive findings were reported in 47 per cent of the severe pre-eclampsies, 77 per cent of the severe vascular-renal group, and 39 per cent of the hypertensive group. The lesions in the patients with pre-eclampsia have always disappeared by the end of two weeks, in contrast with the retinal changes in the other groups which are permanent.

Stander, Herrick, Adair, and other investigators have made similar observations as to age, parity, blood pressure, etc., but so far as we know, no one has been able in as large a series as ours to demonstrate such marked differences between the various groups.

The following findings, previously reported by us, were also noted in the patients comprising this study: chemical changes in the blood, such as lower hemoglobin, cell volume and serum protein concentration in the pre-eclamptic group than in the other groups; marked decreases in the concentration of these constituents after delivery, or clinical improvement in the pre-eclamptic group and little or no change in the other groups.

There is a 15 per cent increase in the blood volume of pre-eclamptic patients and a 30 per cent increase in that of eclamptic patients after delivery. These changes are also associated with clinical improvement without delivery. There is only a 5 per cent increase in the blood volume after the delivery of normal pregnant patients and of those with vascular-renal disease. These differences in blood and plasma volume changes also indicate that all toxemias of pregnancy are not alike.

The mean urea clearance was 60.5 per cent for pre-eclamptic patients and 58.6 per cent in the vascular-renal patients, thus indicating that a large number of these women have no renal impairment. The average volume of urine per hour under test conditions was 41.4 c.c. before delivery and 72 c.c. postpartum in the pre-eclamptic group, and 50.9 c.c. and 73.2 c.c., respectively, for the vascular-renal. Since identical conditions were used for all tests, it is apparent that pregnancy causes a decreased or delayed output of water.

Data from repeat pregnancies are given in Table II. Two hundred ninety-seven deliveries were observed in 137 patients. We have repeatedly noted that the severity of the condition may be different in a subsequent pregnancy. If gestation accelerates hypertensive disease the blood pressure, etc., should reach a higher level with each pregnancy. This usually occurs and the patients are therefore always advised to have a resection of a portion of the Fallopian tubes. Those who become pregnant again have usually refused or have not been offered contraceptive advice or sterilization. Furthermore, our method for determining the degree of severity is a crude one. It is easily possible for the pathologic process to have advanced and yet our determinations of blood pressure, renal function, ophthalmoscopic examination, etc., show no change. In addition to the group of vascular-renal and hypertensive patients, 66 normal pregnancies occurred in 58 patients whom we had

vulsions are imminent. Only a few of the patients in the mild group had symptoms. This is to be expected because one of our criteria for a severe case was the occurrence of symptoms. Table I illustrates the fre-

TABLE I. OCCURRENCE OF VARIOUS GROUPS OF SIGNS AND SYMPTOMS, PER CENT*

	MILD			SEVERE		
	PRE-ECLAMPSIA	VASCULAR-RENAL	HYPER-TENSION	PRE-ECLAMPSIA	VASCULAR-RENAL	HYPER-TENSION
H, P, E, and S	4	3	1	46	33	18
H, P, and E	45	38	13	31	24	23
H and P	17	31	39	5	19	25
H and E	17	10	8	5	1	4
H, P, and S				4	11	11
H	6	10	38		5	11
H, E, and S					3	
H and S			1		2	8
P and E	10	6		9	2	
Miscellaneous but no hypertension	1	2				

*H, Hypertension. P, Proteinuria. E, Edema. S, Cerebral, visual, gastrointestinal, or renal symptoms.

quency of symptoms in combination with the other signs. Since they were always associated with a hypertension, it is logical to assume that the symptoms are most likely due to a vascular spasm, resulting in tissue anoxemia or edema, or perhaps both.

It is noteworthy that a hypertension was the most frequent sign, occurring in 90 per cent of the patients. We have always stressed the point that the blood pressure must be individualized. For example, if a patient with a normal systolic pressure of 90 showed an increase of 35 mm. during pregnancy, this would be a hypertension for her. If we had these data available, we believe that almost all of our patients would have had either a relative or absolute hypertension.

Data as to the time of onset of the toxemia are of interest. Pre-eclampsia did not occur before twenty weeks' gestation and only 14 per cent of the patients had it before thirty weeks. In the other two groups 14 per cent of the patients in each group had the disease before the twentieth week and 42 per cent had it before the thirtieth week. Thirty-seven per cent of the pre-eclamptic patients had signs of toxemia before the thirty-sixth week as compared with 56 per cent of the vascular-renal group. Thus, "toxemia" in the first thirty weeks of pregnancy is almost always vascular-renal disease, essential hypertension, or acute glomerulonephritis. Our data demonstrate the well known fact that pre-eclampsia is a disease of the last trimester of pregnancy.

Only 7 per cent of the pre-eclamptic group were delivered before the thirty-sixth week in contrast to the other groups in which 22 per cent and 16 per cent were delivered before thirty-six weeks. Fourteen per cent of the severe pre-eclamptic and 43 per cent of the severe vascular-renal and essential hypertension groups were terminated before thirty-six weeks' gestation.

Ophthalmoscopic examination, even though made by an experienced ophthalmologist, has been of little aid to us in either diagnosis or prog-

blood pressure or proteinuria between pregnancies and a definite exacerbation in subsequent pregnancies. It is interesting to note that only one-fourth of the patients with toxemia were normal in subsequent pregnancies. This figure should be much larger, because undoubtedly many patients with a history of toxemia were not referred to the toxemia clinic if the pregnancy under observation was normal. The very fact that a certain percentage of patients had no residual pathology and had no recurrence in subsequent pregnancies indicates that the toxemia of pregnancy itself is probably not the cause of a persistent hypertension. Furthermore, 85 of our patients who had toxemia gave a history of a previously normal pregnancy. This would seem to indicate that other factors, such as age, diet, weight, habits, climate, etc., were the predisposing factors rather than an inherent tendency or weakness of the vascular-renal system.

Table III lists pertinent data about the fetus. In most instances fractions have been dropped.

TABLE III. FETAL RESULTS, PER CENT

	MILD			SEVERE			TOTAL
	PRE-ECLAMP-SIA	VASCU-LAR RENAL DISEASE	ESSEN-TIAL HYPER-TENSION	PRE-ECLAMP-SIA	VASCU-LAR RENAL DISEASE	ESSEN-TIAL HYPER-TENSION	
<i>A. Fetal Mortality</i>							
Alive	94	88	94	88	63	79	87
Dead	6	12	6	12	37	21	13
Induced dead	3	7	4	10	32	10	8
<i>B. Induction of Labor and Termination of Pregnancy</i>							
Total induced	26	36	21	56	67	52	36
Per cent of induced dead	10	21	21	18	49	20	24
<i>C. Weight of Dead Fetuses</i>							
Less than 1,000 gm.	0.6	4	0	4	17	4	4
Less than 2,000 gm.	1.4	6	0	11	25	24	7
Less than 3,000 gm.	2.0	8	0	13	30	24	8
<i>D. Weight of All Babies</i>							
Less than 1,000 gm.	1.4	6	0	11	25	24	7
Less than 2,000 gm.	5.0	10	1	18	37	28	11
Less than 3,000 gm.	34.0	33	29	60	70	69	44

"Dead" in Part A includes all unintentional and therapeutic abortions, pre-viable, premature, macerated, stillborn, monstrosities, and neonatal deaths. In other words, if the patient did not have a baby living at two weeks post partum, the fetus was considered dead. This concept of reporting fetal mortality is at variance with the usually accepted method of eliminating abortions, fetuses which are pre-viable or macerated, and monstrosities. We believe that vascular-renal disease frequently and essential hypertension less frequently may be the cause of abortions, premature labor, and intrauterine death of the fetus, and that the seriousness of these various toxemic conditions can best be demonstrated by the use of uncorrected figures. Our data, Part A, indicate that the fetal mortality of the mild vascular-renal group is double that of the pre-eclamptic group. Twelve per cent of the fetuses in severe pre-eclampsia were dead, as compared with 21 per cent dead in the essential hyper-

TABLE II. REPEAT PREGNANCIES WITH TWO OR MORE DELIVERIES IN OUR CLINIC

	NO. OF PATIENTS	NO. OF SUBSEQUENT TOXEMIC PREGNANCIES
Vascular-renal disease:		
Mild	56	68
Severe	10	8
Total	66	76
Essential hypertension:		
Mild	7	7
Severe	1	1
		NO. OF SUBSEQUENT NORMAL PREGNANCIES
Pre-eclampsia:		
Mild	51	
Severe	7	
Total	58	66

REPEAT PREGNANCIES WITH ONE OR MORE DELIVERIES IN OUR CLINIC

	NO. CASES	PRESENT PREGNANCY	
		NORMAL %	TOXEMIA %
Previous history of eclampsia	44	32	68
Previous history of toxemia	218	25	75
Total	262	26	74
Previous normal pregnancy	85		100

previously treated for pre-eclampsia. These patients were watched more closely than usual in the subsequent pregnancy as regards weight gain, blood pressure, and proteinuria, but the pregnancies were normal in all respects. It is possible that the toxemia might have recurred if the patients had not been given special prenatal care. An additional small group of patients is of interest. Five women were observed in 10 normal pregnancies and then each of these in a subsequent pregnancy developed pre-eclampsia. Three were classified as mild and two as severe. In view of these series of patients with pre-eclampsia which was followed by normal pregnancy and normal pregnancy followed by pre-eclampsia, it is difficult to believe that these patients have an inherited tendency to toxemia or that they have a renal or vascular system which has either suddenly become unable to carry the load of pregnancy or suddenly returned to normal. It is also difficult to believe that the toxemia had been caused by a pyelitis or pyelonephritis which was either completely cured in one series or suddenly developed in a second group. It seems to us that we must consider pre-eclampsia an entity distinct from vascular-renal disease and essential hypertension.

We think that the cases reported in this table alone demonstrate that there are at least two large groups of so-called toxemias of pregnancy. The patient with pre-eclampsia recovers completely and has no persistence of hypertension, edema, or proteinuria between pregnancies or recurrence in subsequent ones. The patient with essential hypertension or vascular-renal disease almost invariably has an abnormal

obvious that the cause of death in the majority of our patients was similar to that reported for vascular-renal disease in the nonpregnant; namely, cerebral hemorrhage, cardiac failure, or uremia. Autopsies were performed on 64 per cent of our patients and confirmed our clinical observations. The pathologist was unable to decide in one case as to the etiology of the renal lesions, that is, whether they were caused by a glomerulonephritis or a nephrosclerosis or both.

During the period from 1931 to 1937 we have had over 1,200 toxemic deliveries, an incidence of 7.5 per cent. They have been classified, using criteria previously described as follows: pre-eclampsia total 47.4 per cent (mild, 25.7 per cent; moderate, 15 per cent; severe, 6.7 per cent); vascular-renal disease total 35.8 per cent (mild, 12.5 per cent; moderate, 11.3 per cent; severe, 12 per cent); essential hypertension total 12 per cent (mild, 6.2 per cent; moderate, 3.4 per cent; severe, 2.4 per cent); eclampsia 4.4 per cent; acute glomerulonephritis 0.5 per cent. Mild in the present paper comprises both the mild and the moderate groups.

Kellogg of the Boston Lying-in Hospital states that 87 per cent of their toxemic patients had pre-eclampsia, 2 per cent eclampsia, and the remainder had disease of the vascular or renal system.

Stander reports the following distribution: low reserve kidney, 61.8 per cent; chronic nephritis, 17.9 per cent; unclassified toxemia, 10 per cent; pre-eclampsia, 7.8 per cent; and eclampsia, 2.5 per cent.

Despite a difference in terminology for these various conditions, there should be a comparatively close agreement for the various groups. Our data cannot be reconciled with Kellogg's report, but they do check in part with Stander's. Our pre-eclamptic patients far outnumber his, but if half of his low reserve group are considered as having mild, or Group 1 pre-eclampsia, which he admits is possible, and the remainder as belonging to the vascular-renal or hypertension group, the figures will check. Kellogg's figures are based on hospital diagnosis. It is the general experience that if the type of toxemia is diagnosed only on the hospital records, many patients will be classified wrongly as pre-eclampsia. Our toxemia clinic has been functioning for almost seven years, and we attempt to follow our patients until they die. This may explain in part the distribution of our cases.

On several occasions the first pregnancy was diagnosed pre-eclampsia, with no evidence of vascular-renal disease after the puerperium. The second pregnancy, however, and in a few cases, subsequent pregnancies also showed a recurrence of the toxemia. The diagnosis, of course, is vascular-renal disease for all pregnancies. There is nothing inconsistent with this diagnosis, as after acute glomerulonephritis the blood pressure and urine may, according to the usual tests, be normal for years and then become abnormal again. Similarly, patients with a labile blood pressure may, under abnormal mental stress or in association with infection, have a hypertension which subsequently subsides, to recur again months or years later and then be permanent.

tension and 37 per cent dead in the vascular-renal groups. These figures confirm our belief in our method of reporting fetal mortality for toxemic patients. It is of the greatest importance to the patient and to the doctor to know that if the diagnosis is severe toxemia, over one-fifth of the pregnancies will not terminate with a live baby. It must be remembered that the patient consults her doctor not for a diagnosis but for a live baby. The "induced dead" means that that percentage of the dead resulted from a termination of the pregnancy by therapeutic abortion or induction of labor. It is striking in the severe group that the major portion of the deaths, 10 per cent out of 12 per cent for pre-eclampsia and 32 out of 37 per cent for vascular-renal disease, occurred where the pregnancy was interrupted.

Part B lists data concerning the interruption of pregnancy. All therapeutic abortions are included. The percentage of induced dead means that that percentage of the total number of patients induced left the hospital without living babies. Fifty-six per cent of the patients with severe pre-eclampsia had the pregnancy interrupted, and 18 per cent of the fetuses were lost. Pregnancy was interrupted in 67 per cent of the patients with severe vascular-renal disease, and 49 per cent of these fetuses were lost. There must be a difference between two conditions.

Part C lists the weights of the dead fetuses. These figures are interchangeable with those of Part A, and one can easily determine the number of previable fetuses. For example, the fetal mortality for the severe vascular-renal group is 37 per cent but 17 per cent of these dead fetuses weigh less than 1,000 gm. Therefore, a corrected fetal mortality would be 20 per cent. This figure can be lowered still more by deleting those cases where the fetus was macerated or died because of congenital abnormalities. However, we are not concerned with corrected statistics but with live fetuses or successful pregnancies. The severe group demonstrates beyond doubt that toxemia is associated with small babies. We are cognizant of the fact that over one-half of these pregnancies were terminated prematurely, which would result in a higher percentage of small babies than normal, but again we must stress the fact that these pregnancies were interrupted in the interest of both the mother and unborn fetus. If delivery had not been forced when it was, many of the fetuses would undoubtedly have been born within a few days or a week without material change in weight and some would have been stillborn.

Part D lists the weight of all babies. Approximately two-thirds of all patients with severe toxemia have babies which weigh less than 3,000 gm. Thirty-seven per cent of those with severe vascular-renal disease have babies weighing less than 2,000 gm. Even though many of these small babies are perhaps more immature than premature, yet the probabilities of the mother having a live baby on discharge from the hospital must be carefully considered.

There have been 16 maternal deaths, of which we know, occurring over a period of seven years. One pre-eclamptic patient died as the result of a gall bladder operation three months post partum, and another died from puerperal infection. The remaining deaths all occurred in patients with vascular-renal disease. Cardiac failure was the cause of death in 4 patients, 3 during the early puerperium, and 1 within one year post partum, and a contributory factor in another death. Cerebral hemorrhage caused death in 3 patients, 1 within one year and the others over two years after delivery. Six deaths were due to uremia, 1 within two months and the other 5 within two years. Two of the latter were due to destruction of kidney tissue by pyelonephritis, but the clinical picture of hypertension, renal impairment, etc., was identical with that seen in vascular-renal disease caused by hypertensive arterial disease. Two other patients died within two years of uremia due to chronic glomerulonephritis. One death was caused by acute glomerulonephritis. Our immediate maternal mortality is 4 or 0.36 per cent. The total known death rate over a period of years amounts to 1.3 per cent. It is

TABLE V. ESSENTIAL HYPERTENSION

M. D. (91383), a 23-year-old primipara. Term May 12, 1934. Admitted to hospital on Feb. 25, 1934 because of abruptio placentae. Spontaneous delivery of a 1,100 gm. fetus which lived. On Sept. 4, 1934 when the patient was six weeks pregnant, an abdominal hysterotomy and tubal ligation were performed. Ophthalmoscopic examination: Feb. 28, 1934, normal; Sept. 3, 1934, hypertensive neuroretinitis. In 1936 she had severe epistaxis; blood pressure was 196/130; and there were proteinuria and casts in the urine.

DATE	WEIGHT	BLOOD PRESSURE	ALBUMIN	EDEMA
10/ 5/33	49.5	110/80	0	0
10/28/33	51.1	170/105	0	0
1/ 9/34	54.0	148/114	0	0
1/30/34	55.2	130/110	0	0
2/25/34		210/150	0	0
4/25/34	53.0	150/100	0	0
6/ 5/34	51.8	220/150	0	
9/ 4/34	49.0	194/134	0	
9/28/34	46.2	240/126	0	0

DATE	HEMOGLOBIN GM. %	HEMATOCRIT %	SERUM PROTEIN GM. %	NONPROTEIN NITROGEN MG. %	BLOOD UREA NITROGEN MG. %	UREA CLEARANCE % OF NORMAL
2/26/34	11.8	43	6.3	20	8	51
6/19/34		49	7.2	27	12	52
9/ 3/34	14.0	43		27	13	56

with iodine. The treatment of pre-eclampsia and eclampsia with thyroxin, as suggested by Küstner, is at variance with the above findings. Thyroid therapy has been of no value in the treatment of pre-eclamptic patients.

DISCUSSION

We believe that we have been able to demonstrate that there are several groups of so-called "toxemias of pregnancy," which differ from each other in many ways. Obstetricians have recognized these differences for years, but have failed to agree on a common nomenclature. The term is, unfortunately, an all-inclusive one, and is applied to any pregnant patient who has any of the following symptoms or signs: hypertension, edema, proteinuria, convulsions, vomiting of early or late pregnancy, jaundice, neurologic and mental symptoms, pruritus, dermatitis, etc. Much of the confusion in classification is due to this lack of definition of the term.

"Toxemia of pregnancy" should mean the occurrence of one or more of the following signs in a pregnant woman: hypertension, edema, proteinuria, or convulsions. The term, when possible, should be restricted to pre-eclampsia and eclampsia. All other conditions in pregnancy which are associated with any or all of these signs should be classified as essential hypertension, vascular-renal disease, acute glomerulonephritis, etc.

Essential data for a case of pre-eclampsia are given in Table IV. This patient was selected because we first thought that she had vascular-renal disease in view of her parity and retinal pathology. However, her subsequent course demonstrates that the condition must have been pre-eclampsia.

TABLE IV. BASAL METABOLISM (44575). PRE-ECLAMPSIA

DATE	WEIGHT KILO	EDEMA	PRO- TEIN- URIA	BLOOD PRES- SURE MM.	COMMENTS
1929					First pregnancy, normal
8/19/31	80	0	0	110/ 64	Second pregnancy. Patient 24 yr. old, at term 1/15/32, Hb. 11 gm. %. 9 prenatal visits
10/27/31	86	+	0	110/ 66	Diet instructions
12/ 1/31	89	++	+	138/ 84	
12/29/31	92	+++	+++	160/ 92	Hospital; cerebral and visual symptoms, Hb., 9.1 gm. %; cell volume, 32%; serum protein, 5.7 gm. %; nonprotein nitrogen, 26 mg. %
12/30/31		+++	+++	162/102	Ophthalmoscopic: Acute retinitis, intravenous 20% glucose in 1,000 c.c. amounts
12/31/31		++++	+++	180/120	Induced labor by R.M. and gauze pack, 2,340 gm. live fetus
2/24/32		0	0	122/ 78	Hb., 6.5 gm. %; cell volume, 27%; serum protein 6.2 gm. %; urea clearance, 36%
2/22/33	85	0	0	105/ 65	Third pregnancy, at term 9/2/33, Hb. 11.9 gm. %
9/24/33	90	0	0	130/ 90	Spontaneous delivery, 3,970 gm. fetus, 12 prenatal visits
1/16/34	86	0	0	112/ 74	Fourth pregnancy, at term 8/25/34, Hb., 11.5 gm. %; cell volume, 41%
2/13/34	87	0	0	98/ 60	Ophthalmoscopic: Normal. Urea clearance, 95%
9/ 4/34		0	0	108/ 70	Hb., 12.7 gm. %; cell volume, 39%; serum protein, 7.4 gm. %; urea clearance, 71%
9/12/34	90	0	0	134/100	Spontaneous delivery, 3,285 gm. fetus, 15 prenatal visits
10/21/34	87	0	0	120/ 90	
5/ 9/38	93	0	0	95/ 60	Urea clearance 100%. Hb., 13.4 gm. %; serum protein, 7.2 gm. %

Table V contains data for a patient with essential hypertension which was either of short duration or first manifested itself during pregnancy. The persistently high blood pressure, absence of proteinuria, low normal urea clearance, etc., clearly indicate that the patient had an essential or primary hypertension.

The hypertension which may occur in patients with hyperthyroidism quite often causes confusion. This disease was present in 1.9 per cent of the pre-eclamptic, 1.6 per cent of the vascular-renal, and 7 per cent of the essential hypertension group. Eisele and Ricketts of our Medical Department have stated that the blood pressure remained constant or showed appreciable decreases in many of these patients when treated

Vascular-renal disease is found most frequently in multiparas who are older than thirty and overweight. Two-thirds of these patients also have their signs and symptoms before the thirty-fourth week of gestation. This disease is usually caused by a long-standing essential hypertension, chronic glomerulonephritis, or pyelonephritis.

A systolic blood pressure of 140 mm. or more is the most frequent sign of beginning toxemia, occurring in at least 90 per cent of the "toxemias of pregnancy." The systolic blood pressure in pre-eclampsia is usually less than 180 mm. and rarely over 200. The majority of the patients in the other two conditions have a systolic pressure over 180 and many over 200.

A weight gain of over 0.6 kilos per week is indicative of the possible onset of pre-eclampsia or vascular-renal disease. If this gain is long-continued, subcutaneous edema usually develops.

Proteinuria, unless the twenty-four-hour excretion amounts to 5 gm. or more, is of no significant value for diagnosis or prognosis.

The marked changes in blood and plasma volume, hemoglobin, cell volume, and serum protein concentration that occur in pre-eclampsia, in contrast with vascular-renal disease, also indicate that these are two separate and distinct diseases.

Hypoproteinemia was not a factor in causing toxemia, because the average concentration of the serum protein was 6.2 in pre-eclampsia, 6.7 in eclampsia, and 6.7 gm. per cent in patients with vascular-renal disease.

Toxemia does result in smaller babies. Eleven per cent of all the toxemic babies weighed less than 2,000 gm. and 44 per cent weighed less than 3,000 gm.

The fetal mortality of severe pre-eclampsia is 12 per cent; of severe essential hypertension, 21 per cent; and of severe vascular-renal disease, 37 per cent. The fetal mortality for all cases is 13 per cent.

The major portion of the maternal deaths occurred in the vascular-renal group over a period of years after delivery. They were due to cardiac failure, cerebral hemorrhage, or uremia.

We suggest that an abstract of each case of toxemia be sent to a central registry. Thus, in a short time, sufficient material would be available to permit proper evaluation of etiology, classification, and treatment.

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Whether or not these particular terms are used is immaterial. The point is that further progress will only be possible when everyone doing investigative work is cognizant of the data and knowledge already available.

The proper diagnosis of these conditions is more than academic. The treatment, prognosis, and fetal mortality, and not infrequently, the maternal mortality depend on a proper diagnosis. For example, we hospitalize pre-eclamptic patients when the systolic blood pressure is 160 and quite often even with a lower blood pressure, if the weight gain is excessive, if proteinuria suddenly occurs, or if there is marked edema or symptoms. The patient with essential hypertension or vascular-renal disease is hospitalized only when the systolic blood pressure reaches 190 or more, or if the proteinuria is more than 5 gm. per twenty-four hours. Likewise decreased visual acuity or amaurosis in pre-eclampsia has an excellent prognosis, but in vascular-renal disease there is always some permanent impairment of vision.

We now have over 160 patients whom we have delivered two or more times. These records are valuable, but we should strive to obtain in addition the combined records of a pregnancy and proper follow-up, together with the records from school, insurance, and premarital examinations. Such records would be invaluable and would enable us to settle many of these moot points.

Since we cannot agree on a classification of the toxemias of pregnancy, we should establish a central registry similar to that for cancer and bone tumors where a complete abstract of each case would be sent. After a few years sufficient material would be available to permit proper evaluation of etiology, classification, and treatment.

CONCLUSIONS

The term, "toxemia of pregnancy," should be restricted to those abnormal conditions occurring in pregnancy which are characterized by the occurrence of one or more of the following signs: hypertension, edema, proteinuria, and convulsions. These diseases are: eclampsia, 4.4 per cent; pre-eclampsia, 47 per cent; vascular-renal disease, 36 per cent; essential hypertension, 12 per cent; and acute glomerulonephritis, 0.5 per cent.

Eclampsia and pre-eclampsia are distinct disease entities occurring only in pregnant women. They are most likely to occur during the last trimester in primiparas, whose age is less than thirty and who gain weight too rapidly.

The terms, essential hypertension and vascular-renal disease and pregnancy, as used by us, mean that the primary process in both conditions has been, as a rule, a hypertensive arterial disease. The former condition will ultimately become the latter.

Essential hypertension may be present before or develop during pregnancy. It is also found most frequently in primiparas before the age of thirty, but the weight gain is usually within normal limits, and two-thirds of the patients develop their hypertension before the thirty-fourth week of pregnancy.

While I disagree with Dr. Dieckmann on the point mentioned, I feel that otherwise his conception of the several varieties of hypertension of pregnancy is sound. His emphasis on the chronic hypertensive states, essential hypertension and vascular-renal disease, as he calls them, is particularly timely. To us, this group is a more difficult one to treat, particularly if the patient is a primigravida anxious for a baby, and is a more important cause of death, both maternal and fetal, than are the acute toxemias, eclampsia, and pre-eclampsia.

DR. OTTO H. SCHWARZ, St. Louis, Mo.—In considering the so-called nephritic toxemias of pregnancy, it has always been my understanding that the kidney impairment is due to arterial damage sufficient to put out of commission a certain number of glomeruli and bring about finally a kidney functioning like one with chronic glomerular nephritis. If kidney function tests show any great impairment the chances for the fetus are comparatively bad, and it is now our practice to terminate these cases early in pregnancy when they occur.

Dr. Dieckmann has emphasized the group of essential hypertension. Now I wonder whether an essential hypertension so-called, with normal kidney function tests, will have the same effects as do the cases of true nephritic toxemias. Recently I have followed through pregnancy a case of essential hypertension, well known to be such, in a nulliparous woman in whom the blood pressure was 180 systolic. This did not vary at all through pregnancy and her kidney tests were normal throughout. Another case was observed in which the outcome was very favorable and in which even the blood pressure dropped during pregnancy, to rise again subsequently. In treating these cases I believe that until further evidence is gathered, the more conservative attitude should be taken with these cases of so-called essential hypertension.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—When I came to the Sloane Hospital, now nearly twelve years ago, I found that Dr. Herrick, under the late Dr. Studdiford, had been making a study of the cases of late toxemia. Very soon after that Herrick began classifying these cases, just as Dr. Dieckmann has done today, into essential hypertension, nephritides, and pre-eclampsies. All of us associated with Dr. Herrick have become more and more certain that his is a workable classification.

As has been said, it is not always possible to classify the case when first seen, or even for sometime afterward, but the very long follow-up which Herrick has now had has convinced him that the great majority are primarily vascular cases. The first lesion is a vascular one and this may be followed by kidney complications as the vessels of the kidney become affected. Practically all autopsies which have been obtained on women dying after exhibiting those symptoms during a pregnancy have shown vascular lesions. So we have been convinced for a great many years now that this classification which Dr. Dieckmann has given us tonight is the most workable one we have been able to get so far.

DR. FRED L. ADAIR, CHICAGO, ILL.—I approve very heartily of Dr. Dieckmann's classification. In 1923 I grouped the cases of hypertension during pregnancy into four main groups, recognizing, however, that there was no fundamental difference between pre-eclampsia and eclampsia. The eclamptic and the pre-eclamptic group showed the usual rises in blood pressure which dropped almost to normal, but in certain cases it persisted after delivery. There was one rather unusual group of hypertension, with a pre-existing high blood pressure which showed no increase during pregnancy. Then there was another group with pre-existing hypertension with a superimposed pre-eclamptic hypertension.

Certain case histories illustrate these differences. The first patient was seen in early pregnancy with a history of eclampsia in a previous pregnancy. She was observed in the fourth month of the second pregnancy with a hypertension which then gradually rose, fell after delivery, and then after six months rose again. Her blood pressure continued high for some time but gradually dropped to a pressure somewhat higher than in early pregnancy and continued over a period of years at this level. The patient is still living.

DISCUSSION

DR. JOHN W. HARRIS, MADISON, WIS.—Some fifteen years ago we studied a series of cases of the so-called late toxemias of pregnancy and followed them for at least a year after delivery. In more than one-half of those in whom the diagnosis of pre-eclamptic toxemia and eclampsia had originally been made we found evidences of permanent vascular and renal damage. We were unable to ascertain in most instances whether the original diagnosis was incorrect or whether a primary toxemia of pregnancy had been the causative factor in the production of the permanent damage to the vascular and renal systems. Subsequent studies by other investigators have indicated similar results.

Many attempts, as Dr. Dieckmann has stated, have been made to improve the classification of the late toxemias with varying results, but all of them have left much to be desired. With the patient before us it is often impossible to determine the proper group regardless of the classification one is following. This is not only unfortunate from the standpoint of the welfare of the patient, but the numerous classifications have created a veritable chaos in the literature on the subject. It is often difficult to compare reports of various authors because of the confusion of terms.

The classification which Dr. Dieckmann advocates seems more logical than those that have preceded it, and it certainly is more in accord with modern medical and pathologic concepts. Only time will tell its correctness. However, there still remains the problem of whether those cases thought to be vascular or renal are primary or secondary to a process instituted by pregnancy itself.

Dr. Dieckmann's advocacy of a central toxemia registry deserves serious consideration. Perhaps a large number of case histories submitted by various clinics to a central registry and there thoroughly studied and analyzed might well be of real value in improving the classification of these complications, as well as shedding additional light on their proper treatment.

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—Dr. Dieckmann apparently believes that eclampsia and pre-eclampsia play no role in the production of chronic hypertension. This is at variance with our experience, since about one-third of our cases of pre-eclampsia and eclampsia show hypertension a year later. The reason for this discrepancy lies, I believe, in the fact that Dr. Dieckmann distinguishes between the acute and chronic varieties of hypertension entirely on the basis of his findings six weeks post partum.

For instance, if a patient in the last month of pregnancy develops sudden hypertension, albuminuria, and edema, and all these signs have disappeared at the six-weeks return visit, the case is called by him pre-eclampsia. If, however, the hypertension, let us say, has not disappeared, the case is classified as essential hypertension. She may well have had essential hypertension at the six-weeks return visit but the pertinent question is: what did she have during the last month of pregnancy? It is my feeling that she had pre-eclampsia which resulted in chronic hypertension.

Now let us suppose on the other hand that the condition of this hypothetical case became worse prior to delivery and convulsions supervened. Then if she showed hypertension six weeks post partum, we would not classify the case as essential hypertension, but would say that she had eclampsia which resulted in chronic hypertension.

I realize that the tendency to classify the toxemias some weeks post partum is rather general, but this practice overlooks entirely the fact that the chronic hypertension seen at the six-weeks return visit may be the result of the acute toxemia sustained during the last month of pregnancy.

Just as chronic hypertension represents a chronic vascular process, we believe that the acute toxemias represent an acute vascular process in the form of a vessel spasm which, if allowed to continue for several weeks or so, results in permanent structural injury to the vessel wall, arteriolosclerosis and consequent hypertension. This question is of great practical importance since it obviously has a bearing on the optimum time to terminate pregnancy in cases of pre-eclampsia.

We agree with Dr. Schwarz that, if on *repeated tests* there is obvious renal impairment, the pregnancy should be terminated. He mentions one patient with essential hypertension who had no increase in blood pressure during her pregnancy. We have had six similar patients of whom we know. These cases are rare because, as a rule, the hypertensive symptoms and signs are intensified. The accompanying chart gives an excellent example of a patient with a very labile blood pressure which did not increase during pregnancy, even when an acute pyelitis occurred. Within a year, however, the blood pressure was so high and the associated symptoms so marked that the patient had a bilateral splachnicectomy.

Dr. Watson has mentioned Herrick's work. We are familiar with it because he is one of the pioneers. This classification is not original with us but is commonly used by the internist.

The second case is that of a woman who died about four years from the time she was first seen. She came to me in April, 1916 in early pregnancy with hypertension which rose to a high level. The fetus died and the pregnancy was terminated. She became pregnant again later when the blood pressure rose to a higher level than in the preceding pregnancy, and a dead pre-viable fetus was delivered. Following this the systolic pressure rose but the diastolic did not change much. Subsequently she went from bad to worse and died in November, 1919, almost four years after I first saw her. A complete autopsy was not obtained, but we did get the kidneys. The vessels showed marked changes and the case was diagnosed as an arteriolar nephritis.

I believe there is enough evidence at least to justify the classification of pre-eclampsia and eclampsia as being probably the true toxemias of pregnancy. There is no reason why such patients may not have had some preceding vascular disease. These latter conditions may occur independently of pregnancy, but pre-eclampsia and eclampsia are doubtless due to the same cause and one associated with pregnancy.

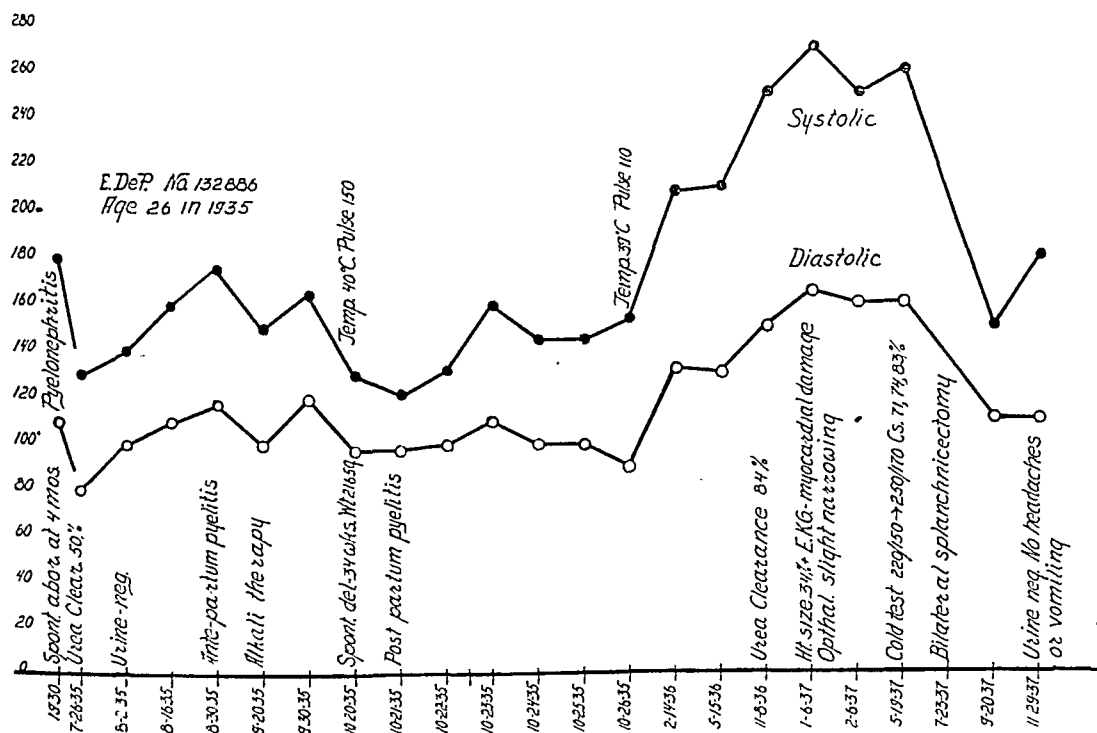


Fig. 1.—E. D., No. 132,886. Patient with essential hypertension, but blood pressure was still labile and did not increase during pregnancy. Marked rise in pressure within one year after delivery, relieved by bilateral splanchicectomy.

DR. DIECKMANN (closing).—Dr. Eastman has raised a question regarding the possibility of permanent damage to the vascular-renal system from eclampsia or pre-eclampsia. Our opinion is not a fixed one, but it seems that a more rational explanation for the presence of hypertension and/or proteinuria one year post partum is that a hypertensive arterial disease was either present before the pregnancy or appeared in a pregnant woman with a predisposition to it. Furthermore, it is not inconceivable that pre-eclampsia and eclampsia might occur in a patient with vascular-renal disease.

Dr. Eastman postulates a patient who at thirty-six weeks begins to have signs of toxemia and who has hypertension when seen one year post partum. I think it highly improbable that this could occur and believe that if the patient had been properly observed during her pregnancy some evidence of an abnormal vascular-renal system would have been noted.

A STUDY OF THE LYMPH GLANDS IN CANCER OF THE CERVIX AND CANCER OF THE VULVA*

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THE spread of cancer of the female genital tract through the tributary pelvic lymphatics was actively investigated in the early years of the present century. Since that time there have been relatively few pathologic studies of this question. Special interest of long standing in the operative removal of lymph glands for certain forms of pelvic carcinoma has enabled me to accumulate considerable material for histologic study. It is the analysis of this material that forms the basis of the present study. Since the number of cases of cancer of the vagina, of the uterine body and of the ovary, in which glands were removed was too small, consideration has been limited to those in which the primary site was in either the vulva or the cervix.

A total of 1,271 lymph glands were subjected to microscopic examination. In the group of cervix cancers, 521 glands were removed, 502 by operation and 19 at autopsy. The 750 glands associated with cancer of the vulva were all removed by operation. The types of operation done in these cases were:

Gland removal with hysterectomy for cervix carcinoma	2 cases
Iliac lymphadenectomy for Group II cervix carcinoma	83 cases
Iliac lymphadenectomy for Group III cervix carcinoma	7 cases
Double-sided Basset gland removal for vulva carcinoma	53 cases
One-sided Basset or incomplete gland removal for vulva carcinoma	12 cases
Autopsy for cervix carcinoma	9 cases

With the exception of the inguinofemoral lymph chain which was excised en masse, each gland was removed separately, and placed in a bottle, labeled as to side and location. In many cases a photographic record of the gross appearance of these glands, size, and location was made shortly after operation. In the vulvar cases the primary tumor was photographed with the glands (Fig. 1). In the cervix cancers, the tubes and ovaries removed at the time of the iliac gland resection were included in the picture (Fig. 2). In this way it was possible to record information concerning the anatomic distribution of cancer metastases in these two groups of tumors and also obtain data concerning the varying histopathology in different groups of pelvic lymph glands. Such systematic studies of glands have not to my knowledge been heretofore made on a large scale.

Our knowledge of the anatomic distribution of the pelvic lymph glands in women has been largely based on careful dissections of the cadaver, at times associated with the injection of some coloring material to outline more clearly the path of the lymph channels and the correlation of the various groups of lymph glands. A study of the numerous

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ureteral gland, also called the gland of Championnier, involved by metastasis. Its removal was by no means simple, at times requiring ligation of the uterine vessels and in one case resection of an adherent portion of the uterine vein. Where this portion of the broad ligament was sclerosed or evidently carcinomatous, no attempt was made to isolate the ureteral gland. Where, however, a careful digital palpation of this area revealed a circumscribed nodule, it was excised.

Out of the total of 1,271 lymph glands removed, the anatomic distribution was as follows: inguinofemoral chain, approximately 540 glands, external iliac glands 212; obturator glands 259; hypogastric glands 253; ureteral glands 7.

In 864 of the 1,271 glands microscopic sections were available for careful histologic study; 483 of these glands were associated with cervix cancer and 381 were in cases of cancer of the vulva. The question of



Fig. 3.

Fig. 4.

Fig. 3.—Hyperplasia of the follicles. Unusual proliferation of the germinal centers, almost simulating a metastasis.

Fig. 4.—Endothelial hyperplasia. Active growth in the elements comprising the reticuloendothelial system including many macrophages.

what is normal and what is pathologic in the histologic structure of lymph glands is one that is far from settled. Pathologists have a tendency to call glands hyperplastic when they might well be looked upon as normal. The size of lymph glands varies greatly in different individuals and in different anatomic locations. Age and obesity play an important role in the normal histologic picture. In attempting to group glands according to the dominant characteristics found, I confess great difficulty in attempting to differentiate between these normal variations and those due to associated pathologic conditions, infection, or carcinoma.

Almost every conceivable variety of lymph gland pathology was to be found in the 864 glands that were reviewed in this study. I attempted in each case to classify the gland according to the dominant

great as has been usually described. My operations did not go so far as to include the sacral glands, situated lateral to the rectum on a level with the sacrouterine ligaments, or the higher common iliac and periaortic glands situated near the sacral promontory. They were limited essentially to the five groups described below:

1. *The Inguinofemoral Lymph Chain*.—From six to twelve glands, occasionally more, were imbedded in the fat and fascia extending parallel to and usually slightly below Poupart's ligament. Along the saphenous veins they were found as low as two to three inches below the femoral ring and several were located in the loose fat of Scarpa's triangle. One or two glands were usually situated in the fascial tissues of the fossa ovalis and almost invariably one gland was pocketed just below the femoral ring, internal and slightly posterior to the femoral vein. This last-named gland, the gland of Cloquet or Rosenmueller, was commonly the site of carcinomatous metastasis. Up to eight years ago, I followed Basset's original technique and cut Poupart's ligament to gain access to this gland, but wider experience convinced me that this was rarely necessary, since with a little care, the gland could be removed completely without risk of injuring the femoral vein, leaving Poupart's ligament intact and thus simplifying the operation.

2. *The External Iliac Glands*.—In every case of vulvar carcinoma and in the majority of cervix cases one or two glands were removed from the iliac fossa external to, and occasionally superimposed on, the external iliac artery just above Poupart's ligament. This gland was invariably imbedded in a considerable mass of loose fat, was rather large, from $1\frac{1}{2}$ to 4 cm. in diameter, soft in consistency, with a definite fibrous capsule. On section it usually consisted largely of fat with a narrow rim of lymphatic tissue.

3. *The Obturator Glands*.—The obturator gland was situated usually about 1 cm. below the external iliac vein running parallel to and often closely attached to the obturator nerve for a distance of 3 or 4 cm. This gland was as a rule rather firm in consistency, long and narrow, with rounded contour. Occasionally a second gland occurred in this location. In fatty individuals it was imbedded in a mass of loose fat adjacent to the obturator nerve. Its upper margin lay close to the origin of the uterine artery and its lower margin just above the femoral ring.

4. *The Hypogastric Glands*.—There was considerable variation in the location of the hypogastric glands. They were usually pocketed in the angle between the external and internal arteries, readily exposed when the broad ligament had been widely opened. Occasionally however they were tucked behind the external iliac vein near its junction with the internal iliac vein. Exceptionally we have found them over the dividing point of the two arteries or between the psoas muscle and the external iliac artery near this junction. There was usually one distinct, rather firm, irregularly ovoid gland, 2 cm. in diameter but, in about one-fourth of the cases one or two additional nodes were found. Technically they were the most difficult to remove, because of their proximity to the large vessels, and the frequency of dense adhesions to these structures. The ureter runs over them but can be pushed aside since it clings to the posterior peritoneal sheath. Cancer metastasis was the most common cause of these adhesions; but in several instances hard, apparently malignant glands were excised with difficulty, only to find on microscopic section that they showed fibrosis but no evidence of carcinoma. In all these cases the patient had received a full course of x-ray therapy before operation and the thought arose that the adhesions may have been due to sclerosis following radiation of a malignant metastasis. In 4 cases adhesions were so dense that a section of the external iliac vein (3 times) or artery (1 time) had to be removed with the gland. In none of these cases did any complicating disturbance of circulation result.

5. *Ureteral Glands*.—In 1903 Sampson called attention to the frequency of microscopic lymph nodes in the broad ligament near the crossing of the ureter and uterine vessels. Occasionally these nodes were larger, up to 1 cm. in diameter, and, especially in cancerous invasion of the cervicovesical septum, it was not unusual to find the

glands were divided into two groups: those that showed definite follicles and those that did not show any such germinal centers. In these three periods of my operative experience, there were marked differences (Table II).

TABLE II

YEARS	FOLLICLES PRESENT	FOLLICLES ABSENT	PER CENT FOLLICLES PRESENT
October, 1930—May, 1934	60	18	77
May, 1934—May, 1936	37	56	40
May, 1936—May, 1938	75	212	26

The marked difference between 77 per cent with follicles in the early group and only 26 per cent with follicles in the last group showed without reasonable doubt that heavy radiation produces marked destruction of the germinal centers. What bearing this may have on the growth or spread of the disease is a matter for debate. On the one hand the lymphocytes are probably an important aid in fighting off the invasion of this disease but on the other hand the sclerosing effect of such treatment on the tributary lymph channels and glands may tend to block its spread to other portions of the body.

In the cervix cases a division of the histologic characteristics according to the three principal locations showed the following interesting differences.

TABLE III

LOCATION	FOLLICULAR	ENDOTHELIAL	HYALINE	FATTY FIBROUS	DIFFUSELY CELLULAR	CALCIFIED	TOTAL
Hypogastric	69	50	34	35	18	1	207
Obturator	23	54	33	49	5	7	171
External iliac	4	16	15	53	4	8	100

The hypogastric glands showed follicular hyperplasia most frequently; the obturator glands were characterized by endothelial hyperplasia with a considerable percentage of fatty fibrous changes, whereas the external iliac glands situated in the loose fat of the iliac fossa were predominantly of the fatty type with fibrous capsule and septa. In many of these fossa glands, there was only a tiny crescent of lymphatic cells and a thin fibrous capsule enclosing a mass of fat.

According to C. Sternberg hyaline degeneration is characteristic of lymph glands in cases of malignant disease. While we had no basis for comparison with normal cases, it was rather striking that in 84 of the cervix cancers and 63 of the vulvar cancers the hyaline changes dominated the histologic picture (Fig. 5), so that frequently only narrow strands or small agglomerations of lymphocytes remained. These hyaline glands comprised 17 per cent of the total number. Senility could hardly

histologic characteristic. In two cases all the glands removed showed the typical picture of a tuberculosis. One was associated with cancer of the vulva and one with a cervix cancer. In the remaining cases I grouped them under follicular hyperplasia (Fig. 3), endothelial hyperplasia (Fig. 4), hyaline degeneration (Fig. 5), fibrous fatty, diffusely cellular, and calcified (Fig. 6). Some difference was noted between the vulvar and the cervix cases as shown in Table I. It will be noted that endothelial hyperplasia was more common in the cervix cases, while follicular hyperplasia and fibrous-fatty changes were noted relatively more frequently in the vulva carcinomas. Since the atrophic changes associated with fibrous and fatty infiltration are characteristic of old age, this difference may be due to this fact, for in cervix cases the average age was about 42 years, whereas in vulvar cancer it was 59 years.

It has been stated by A. M. Welsh and others that radiation treatment produces a destruction of the lymph follicles and this would seem

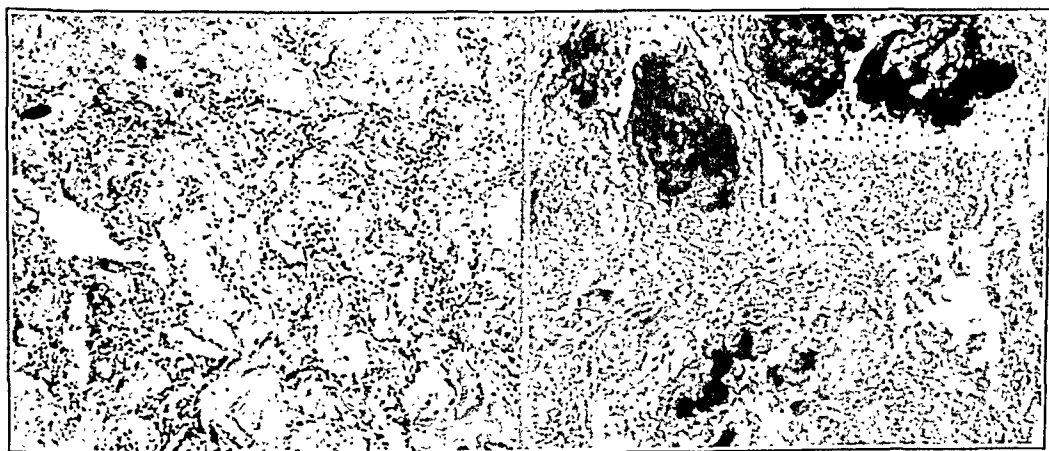


Fig. 5.

Fig. 6.

Fig. 5.—Hyaline degeneration of lymph glands with marked destruction of normal follicles and reticulum, possibly attributable in part to the products of cancer metabolism.

Fig. 6.—Calcification of lymph glands, often a sequel to hyaline changes.

to be confirmed by my observations. In the cervix cases the operative gland removal for the first three years (1930-1934) was usually not preceded by any radiation. In the following two years (1934-1936) the radiation dosage averaged only about 2,400 r. units. In the last two years (1936-38), preliminary radiation was very heavy, averaging 5,600 r. units, and at times associated with a radium dose of 4,500 mg. hr. The

TABLE I

PRIMARY TUMOR	FOLLICULAR	ENDOTHELIAL	HYALINE	FATTY FIBROUS	DIFFUSELY CELLULAR	CALCIFIED	TOTAL
Cervix	96	120	84	137	30	16	483
Vulva	91	62	63	140	10	15	381

clined to interpret other forms of endometriosis of the pelvic organs to lymphatic transport rather than to transtubal implantation according to Sampson. In recent years French writers have again emphasized the occurrence of these epithelial structures in the lymph glands of cervical cancer patients. Michel-Beehet found two endometrial inclusions in 13 cases where glands were removed for cervix cancer. He interpreted them as malignant metastases. Leveuf, Herrenschmidt, and Godard in 36 cases had similar findings and a similar interpretation. Gricouroff on the other hand disproves these conditions of malignancy and found typical endometrial tissue in one out of five cases where glands were removed at autopsy in absolutely normal cases. One recent American contribution to this subject deserves special mention. Hausmann and Schenken in 1933 found two lymph gland endometrioses, one in a 31-year-old woman who had uterine chorioepithelioma and one in a negress dying of nonmalignant causes who had endometriosis of both ovaries as well as in the lymph gland.

In my own series of endometrial implants in the lymph glands, it is significant that none were found in the 381 glands tributary to carcinoma of the vulva. In 90 lymphadenectomy operations for Group II or Group III cervix carcinoma endometriosis was found in 8 cases, three times in two of the glands removed, making a total of eleven glands that showed endometriosis. In addition these structures were found in one hypogastric gland removed at autopsy for cervix carcinoma. There was considerable variation in the microscopic picture in these twelve lymph glands. Sometimes there was a small disc-shaped epithelial inclusion (Fig. 8), sometimes a cystlike structure with irregular contour and epithelial proliferations (Fig. 9), and in two cases the picture resembled closely the morphology of uterine glands (Fig. 10). In all instances the endometrial metastases followed the course of the efferent lymph channels, lying in the large sinuses directly under the capsule of the gland. In none of the 41 out of 90 patients subjected to lymphadenectomy who were over 45 years of age was any endometriosis found. The eight patients operated upon showing endometriosis, all ranged in age from 30 to 42 years. This tends to confirm its relationship with the processes of menstruation. In three patients, both ovaries showed small areas of endometriosis as well as the lymph glands, and in one patient there was in addition to this a double-sided adenomyosis of the uterine portion of the Fallopian tubes. In this last-named patient (Figs. 11 and 12) therefore we found six points of endometrial proliferation, 2 in the ovaries, 2 in the tubes, and 2 in the lymph glands.

By the law of proportion in these 9 cases of lymph gland endometriosis, we should have found cancer metastasis present in one-third of the cases, that is to say in three of them. It so happened, whether by chance or not I cannot say, that in none of the 9 was there such a finding. The coincidence of cancer metastasis and endometrial metastasis has, however, been reported by others. Insufficient data are available at present as to how frequently this occurs.

be held responsible for these changes since they were present in both cervix and vulva cases, in spite of the average age difference in the two groups.

In those cases in which the infected cancerous ulcer had not previously been sterilized by radiation, marked hyperemia of the extirpated lymph glands evidenced either by dilated blood vessels (Fig. 7) or bloody infiltration of the lymphatic tissues, was frequently observed. Such glands were usually large and succulent, often somewhat edematous. Frequently operative wound infection attended their removal.

Without question the most interesting finding in this study outside of the distribution of cancer metastases was the frequency of glands showing endometriosis. As far back as 1898, long before the question of endometrial-like implants in the pelvis had even been thought of, Wertheim found on serial section of lymph glands removed for cervix carcinoma the occurrence of cystlike irregular spaces lined by cylin-



Fig. 7.—Hyperemia of the lymph glands showing marked dilated blood vessels, often found in infected cancers.

dricial epithelium. Since these epithelial structures occurred rather frequently, 48 times in 500 cases (9.6 per cent) of cervix carcinoma and not in a single one of 80 cases free of carcinoma subjected to examination of pelvic lymph glands at autopsy, he concluded that these structures were cancer metastases. Later, when in a second series of 10 autopsies, he found a similar epithelial-like cyst in a patient who died of pelvic infection he retracted his former opinion. Those who opposed Wertheim's views of operative gland removal in cervix cancer brought up a mass of evidence proving that such epithelial proliferations were found in a great variety of conditions not associated with cancer. Schindler in 1906 suggested for the first time a transplantation of uterine epithelium to account for these epithelial inclusions in the tributary lymph glands. The relative frequency of their association with cervix carcinoma was noted by others. Kermauner and Lameris found them in 11 out of 87 cases. Halban and Mestitz in 1926 stressed the endometrial nature of these lymph gland metastases and were in-

by Sampson. May we not assume that a proliferating intracervical carcinoma may similarly block the free exit of menstrual blood and with the lymphatics opened by the ulcer just above the blocking tumor give opportunity for transport of endometrial tissue to the tributary hypogastric and obturator lymph glands. In all of my cases the endometrial metastases were limited to these two groups of lymph glands.

Turning now to the subject of cancer metastases in these lymph glands, we see in Figs. 13 and 14 the anatomic distribution and number found in carcinoma of the vulva and carcinoma of the cervix. The vulvar metastases were found in 30 out of 65 patients operated upon (46 per cent). There were many patients with multiple metastases. The inguinofemoral chain was found involved 40 times, 21 times on the right, 19 times on the left side. In only 5 instances were the deeper glands found involved; on the right side the external iliac twice, the obturator once; on the left side the external iliac and obturator each once. Many



Fig. 11.

Fig. 12.

Fig. 11.—Endometriosis of lymph gland.

Fig. 12.—Ovary from same patient as Fig. 11. In this case two lymph glands, both ovaries, and both tubes showed evidence of endometriosis.

of the larger metastatic glands in the femoral region showed a tendency to central necrosis and those associated with slow-growing well-differentiated cancers were frequently fibrotic. In 10 of the 30 cases with metastases, both sides were involved. In four of the more advanced cases the glands were so firmly adherent to the wall of the femoral vessels that they could not be removed.

In cervix carcinoma metastases were found in 29 out of the 83 Group II lymphadenectomies and in 2 out of the 7 Group III lymphadenectomies. In the latter group technical difficulties made a satisfactory complete operation impossible. We thus have an average of 34 per cent involvement for the entire group and 35 per cent for the Group II series. In 9 patients glands on both sides were involved, and as seen in Fig. 14, the distribution was more varied than in the vulvar cases.

No one has to my knowledge ventured an explanation of the remarkable frequency of lymph gland endometriosis in cervical cancer, approximately 9 per cent of all cases. This thought occurs to me. The importance of cervical stenosis as predisposing to the retrograde flow of the endometrial particles released at menstruation has been stressed

Fig. 8.

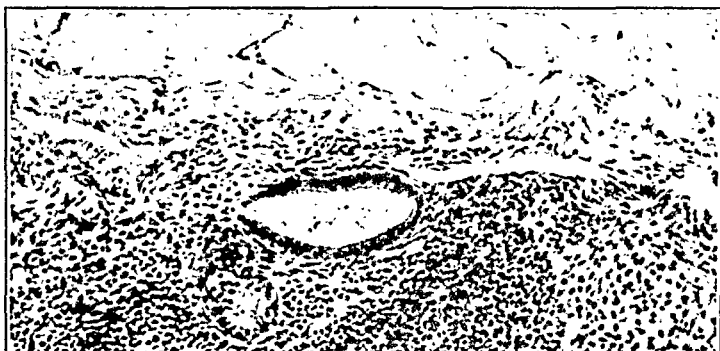


Fig. 9.



Fig. 10.

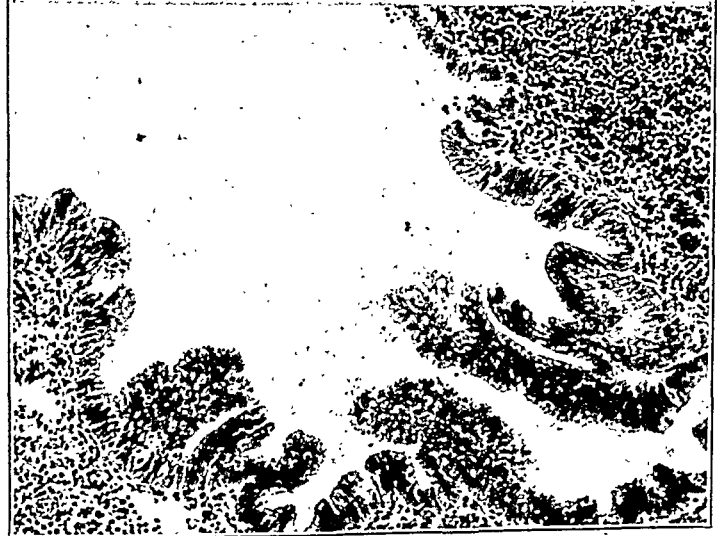


Fig. 8.—Small endometrial implant beneath the capsule of a lymph gland.
Fig. 9.—Epithelium-lined cysts of endometrial origin found in lymph gland.
Fig. 10.—Typical endometrial proliferation in a lymph gland.

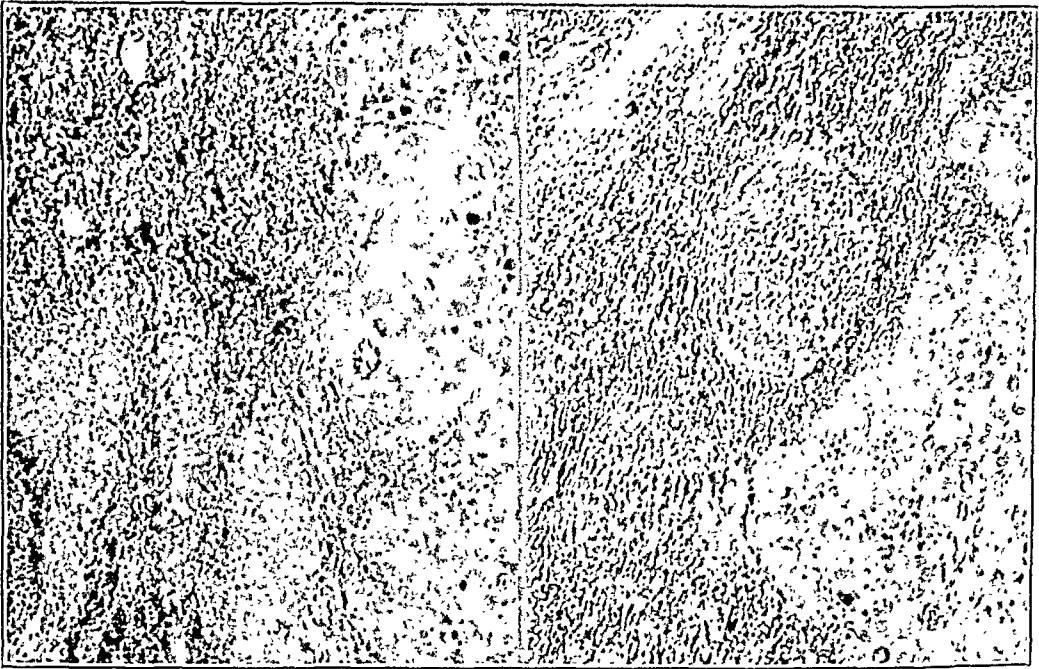


Fig. 15.

Fig. 16.

Fig. 15.—Edge of large subcapsular metastatic carcinoma of lymph gland.
Fig. 16.—Metastatic carcinoma in lymph gland associated with large germinal follicles.

Fig. 18.

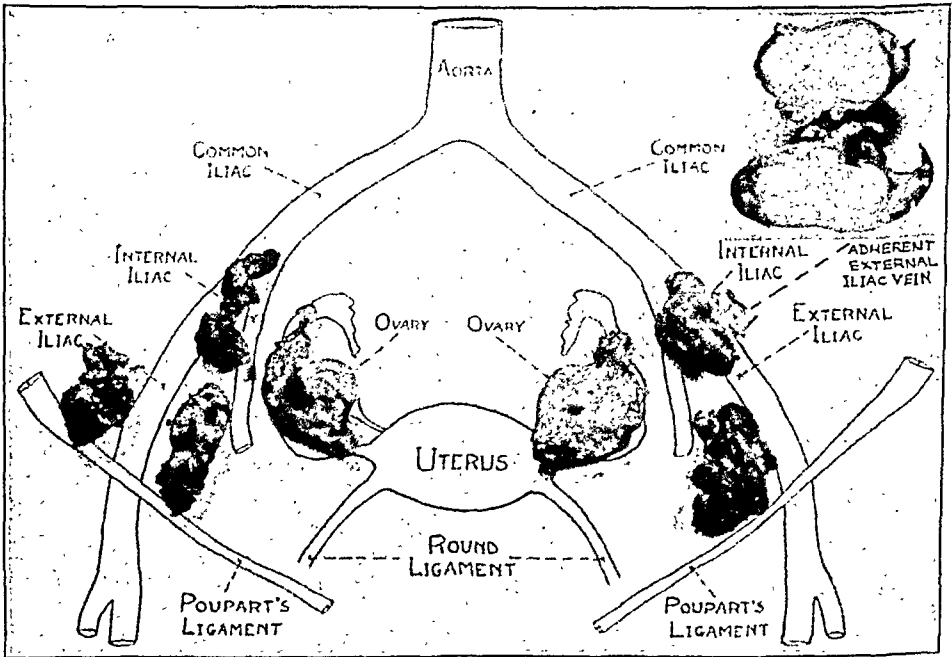


Fig. 17.

Fig. 17.—Anatomic distribution of glands removed in Group II cancer of the cervix. The left hypogastric gland so densely adherent to the external iliac vein as to require resection of this vessel to effect gland removal.
Fig. 18.—Same case as Fig. 17. Cross-section of adherent carcinomatous hypogastric lymph gland.

Noteworthy was the rarity of metastases in the external iliac group, noted only in one patient. The left side was far more frequently the site of lymph gland spread, 30 glands compared to only 18 on the right side. The hypogastric glands were affected 33 times out of a total of 48 carcinomatous glands, an average of 68.75 per cent.

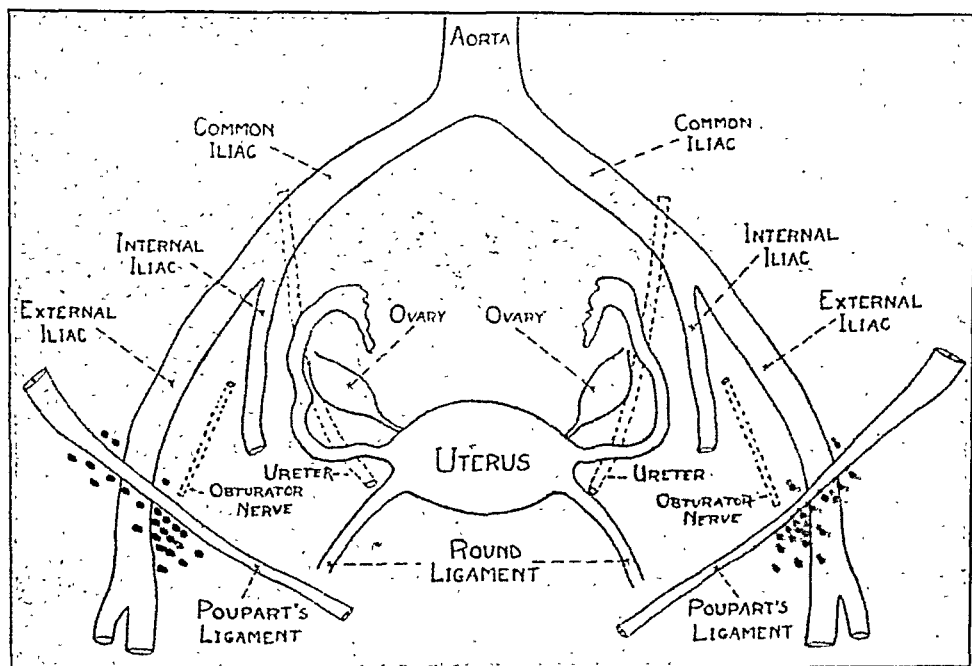


Fig. 13.—Anatomic distribution of cancer metastases in lymph glands associated with vulvar carcinoma: right inguinofemoral lymph chain, 21; left inguinofemoral lymph chain, 19; right external iliac, 2; right obturator, 1; left external iliac, 1; left obturator, 1.

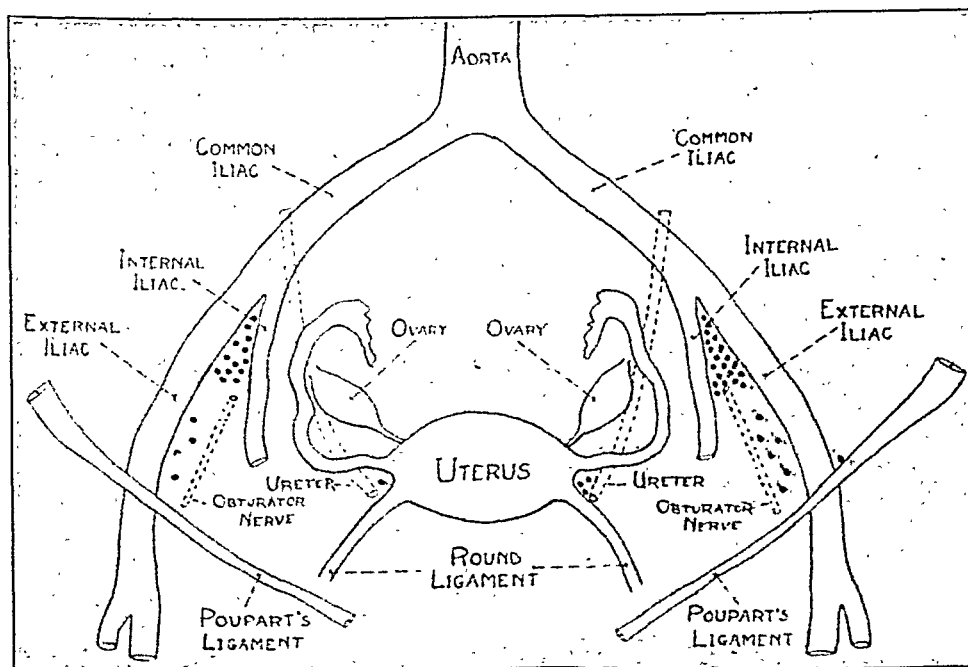


Fig. 14.—Anatomic distribution of cancer metastasis in lymph glands associated with cervix carcinoma: right hypogastric, 13; right obturator, 4; right ureteral, 1; left hypogastric, 20; left obturator, 6; left ureteral, 3; left external iliac, 1.

of the endometrial character of these lesions lies in their association with ovarian endometriosis in three instances. The frequency of lymph gland endometriosis in cervix cancer may possibly be explained by a blocking of the cervical canal with open lymph gland channels above the point of blocking.

Cancer metastases occurred in 46 per cent of vulvar cancers and in 35 per cent of Group II cervix cancers. In vulvar cancer the inguino-femoral chain was most often involved; in cervix cancer it was usually the hypogastric glands.

The operative complications and mortality in these lymph gland operations were relatively slight. Four out of 53 Basset operations ended fatally (7.5 per cent), and only 2 out of 83 patients who had lymphadenectomies for Group II cervix cancer died (2.4 per cent).

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The size of the metastases varied from a microscopic subcapsular nest in the efferent sinuses to huge masses distending the lymph gland and leaving only a narrow rim of lymphocytes beneath the fibrous capsule (Fig. 15). Out of 36 Group II lymph glands showing carcinoma, it was found that 13 were characterized by follicular hyperplasia (Fig. 16), 2 by endothelial hyperplasia, 11 by hyaline degeneration and fibrosis, and 10 by a diffuse structureless distribution of lymphatic tissue. We can therefore make no deductions as to what type of lymph gland is most frequently the seat of cancer metastases. Wherever the metastatic nodule was small and the structure of the gland well preserved, it was evident that the point of entrance was in the capsular sinuses of the efferent vessels.

A few points as to operative complications and mortality in these lymph gland operations may be mentioned. In the vulvar cases where the Basset double-sided gland removal with vulvectomy was the operation of choice, some degree of postoperative wound necrosis occurred in about 90 per cent of the cases. The average age of 59 years and the debility of many of these patients partly accounts for the poor healing. It also was a factor in the mortality rate, which owing to 2 recent postoperative deaths is now 7.5 per cent, 4 out of 53 complete Basset operations with vulvectomy. The lymphadenectomies in cervix cases, although involving a laparotomy, were done in younger individuals. There were only two deaths in 83 Group II cases, or a primary mortality of 2.4 per cent. The chief complication in this group was operative hemorrhage. In two patients this could only be controlled by clamps and a pack which were later removed without complicating infection. In 4 instances the external iliac vessels (Figs. 17 and 18) were ligated or resected with the adherent glands.

CONCLUSIONS

A total of 1,271 lymph glands removed for carcinoma having its primary seat in the vulva or cervix showed a fairly constant anatomic distribution of the tributary lymph channels.

The five groups studied in this series were the inguinofemoral chain, including Cloquet's gland, the external iliac glands, the obturator glands, the hypogastric glands, and the ureteral glands.

In 864 glands of this series, available for further microscopic study, a great variety of histologic changes were noted. Follicle hyperplasia was relatively frequent in the inguinofemoral chain and in the unirradiated pelvic lymph glands. In the external iliac group fatty infiltration was the usual picture.

There was a striking absence of lymph follicles in those glands that had been subjected to heavy preoperative radiation, so that there is little doubt that follicles are destroyed by this treatment.

The frequency of hyaline degeneration points to a possible connection between this pathologic change and the products of cancer metabolism.

Nine cases of endometriosis in the lymph glands indicate a high incidence of this anomaly with cancer of the cervix. Confirmatory evidence

TABLE II. COLLECTED FIVE- AND TEN-YEAR RESULTS OF TREATMENT OF CARCINOMA OF THE CERVIX

	DATE OF TREATMENT	PATIENTS TREATED		FIVE-YEAR SURVIVORS		TEN-YEAR SURVIVORS	
		NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Lynch	1916-1927	186	100	41	22.0	34	18.3
Ward and Sackett	1919-1927	344	100	85	24.7	62	18.0
U. of P. Series	1920-1927	304	100	71	23.3	57	18.7
Totals		834	100	197	23.6	153	18.3

regardless of methods of treatment the five-year survival rate is near 20 per cent. Study of the composite group made up of Ward's, Lynch's, and our cases shows that of 197 patients who survived five years, 77.6 per cent lived ten or more years after treatment.

The second approach to our evaluation of the five-year criterion is concerned with an entirely different group of cases. Of all the patients treated for cervical carcinoma in our clinic from 1913 through 1927 87 with microscopic proof of cancer have survived five or more years. Every patient in this group has been traced to the present time.

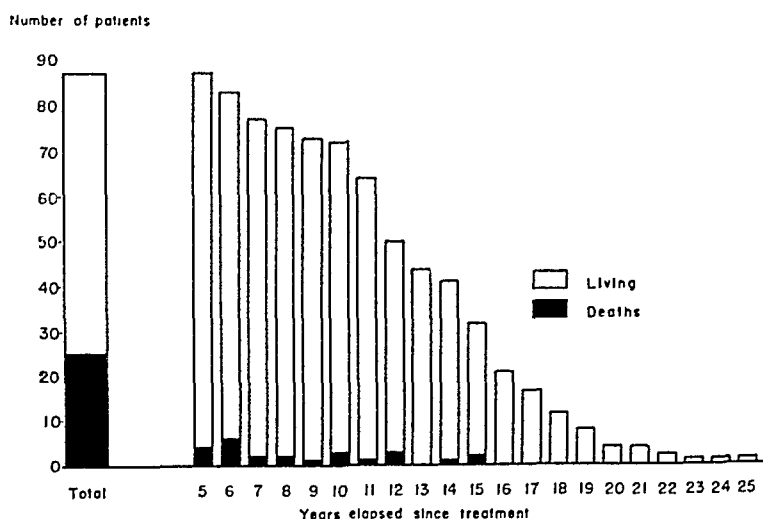


Chart 1.—Mortality subsequent to five-year survival of 87 patients treated, 1913 to 1927.

Chart 1 shows the follow-up data on 87 patients who survived from five to twenty-five years after treatment. The first column shows the total mortality and the following columns depict the time of death subsequent to five-year survival. The total mortality in this group is 29 per cent. Most of the deaths occurred in the second five-year period following treatment. The explanation of this will be found in Chart 2.

Chart 2 presents the causes of death under three categories, (1) from extension or recurrence, (2) from unknown causes, and (3) from causes other than cancer. Sixteen patients (18.4 per cent) are known to have died of cancer. It will be noted that most of these deaths occurred in the second five-year period after treatment. Four other patients have died of unascertained causes; if these four deaths be considered due to cancer, the total cancer deaths in the group are 20 (23.0 per cent). After surviving 12 or more years 5 patients died from causes not related to the

AN EVALUATION OF THE FIVE-YEAR CRITERION IN CARCINOMA OF THE CERVIX*

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THE arbitrary five-year criterion tends to direct interest in the results of radium treatment of carcinoma more toward five-year than toward permanent results. That patients not infrequently die of recurrence of the original growth long after the five-year mark, is a fact well known to all of us. The present study is an attempt to evaluate five-year survival as an index of the permanent cure of cervical carcinoma.

The first approach was to determine the number of patients who survived ten years in proportion to the number of five-year survivors in a group of 304 primary cases of cervical carcinoma treated with radium at the Hospital of the University of Pennsylvania from 1920 through 1927. The series begins with 1920, when Dr. John G. Clark discontinued hysterectomy and adopted radium therapy for all cases of cervical carcinoma. Patients treated since 1927 are excluded so that our ten-year results could be known. Stage V (Schmitz) cases are not included because procedures other than irradiation were employed in their treatment.

Microscopic confirmation of the diagnosis of carcinoma was obtained in all but six of the patients in this series who survived five or more years. It seems unfair to rule out all of the cases in which there was no biopsy, as by so doing 60 advanced fatal cases would also be eliminated and thus falsely raise the percentage of five-year survivors. Follow-up data were obtained in 97.3 per cent of the entire group. The unfollowed cases are included and counted as dead.

TABLE I. FIVE- AND TEN-YEAR RESULTS OF RADIUM TREATMENT OF CARCINOMA OF THE CERVIX (1920-1927)

PATIENTS TREATED	FIVE-YEAR SURVIVORS	TEN-YEAR SURVIVORS
304 (100%)	71 (23.3%)	57 (18.7%)
80 per cent of those who lived five years survived ten or more years after treatment.		

As shown in Table I, 23.3 per cent of the treated patients survived five or more years, and 18.7 per cent of the original group lived more than ten years after treatment. In other words, four-fifths of those who survived five years lived at least ten years after treatment.

In Table II are recorded the five- and ten-year survival rates recently reported by Ward and Sackett from the Woman's Hospital of New York and those of Frank Lynch from the University of California Clinic. Although the latter statistics have not been published, Lynch has kindly given us permission to use them. The striking uniformity of these results confirms William P. Healy's oft repeated statement that

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

DISCUSSION OF PAPERS BY TAUSSIG, AND KIMBROUGH AND TOMPKINS

DR. BROOKE M. ANSPACH, PHILADELPHIA, PA.—Dr. Kimbrough's paper brings out the fact that while five years as an arbitrary period does not indicate the final salvage of patients with carcinoma, it is a very reliable index of the way things are going. His statistics indicate that 71.2 of the five-year salvage and 86 per cent of the ten-year salvage is likely to be maintained.

There must be considerable difference in our attitude toward cancer of the cervix and cancer of the vulva. Vulvectomy followed by a bilateral extirpation of the glands may be likened to that for breast cancer where with the breast and the pectoral muscles the surgeon removes all of the lymph tissue in the axilla. Both of these procedures bear relatively little risk. In both instances the areas are more easily accessible and the mortality is low. It is a different matter with cancer of the cervix, for here there is much more difficulty in the removal of the diseased glands.

Adenectomy supplementing treatment with radium involves certainly less risk when it is confined to the removal of the carcinomatous glands. But a complete pelvic adenectomy must carry with it a higher primary mortality than adenectomy in carcinoma of the vulva.

Dr. Taussig's studies may be interpreted as giving an additional reason for depending to a great extent upon radiation in the treatment of cancer of the cervix, for he found that the larger the dose of radon units the greater the effect upon the lymph follicles in the pelvis. If the lymph nodes are affected, the cancer nests in them are exposed to the same influence and the types of cancer cells amenable to radiation are favorably influenced. This does not mean that radiation destroys the cancer nests uniformly, since they were present in 34 of Dr. Taussig's lymphadenectomies.

His findings relative to endometriosis suggest the probability that the lymph glands of the pelvis are not uncommonly the seat of this disease, and if they are it would lend color to the theory of the direct growth or deportation of the endometrial tissue, either through the lymphatic spaces or the tubes, rather than an explanation of endometriosis on the grounds of an early metaplasia of the cells that originally line the peritoneal cavity.

DR. CHARLES A. BEHNEY, PHILADELPHIA, PA.—Three reports (Ward and Sackett, Lynch, Kimbrough) have independently shown the ratio of the ten-year to the five-year salvage in carcinoma of the cervix treated with radium. The grand total of the three series becomes numerically important. One can now safely expect a ten-year salvage of 75 per cent of the patients who have survived five years. It is interesting in this connection to note that Shaw, reporting a series of 154 patients with carcinoma of the cervix treated by the Wertheim operation, found that 72 per cent of those who survived the five-year period were living and well ten years after operation.

Though less reprehensible it is just as incorrect to depreciate cures as to exaggerate them. It has always seemed unfair to attribute all deaths in patients who have had carcinoma to the disease. If other studies of the cause of death after five years' survival confirm Dr. Kimbrough's findings, a basis for more accurately estimating end results will be available.

It has been stated that high voltage x-ray therapy will not destroy carcinoma cells in the lymph nodes of the pelvis. Those of us who have seen carcinoma in the cervix, the fundus, the ovaries, and throughout the peritoneal cavity melt away after deep x-ray therapy doubt that the discovery of cancer cells in lymph nodes after irradiation proves that in these nodes carcinoma is *never* destroyed by this therapy. Dr. Taussig's observation that the lymph follicles decreased as the irradiation dosage was increased indicates that there is a marked irradiation effect on these nodes. I should like to inquire whether he has a record of the comparative lymph node metastases found with the different irradiation dosages.

original cervical malignancy, viz., (1) Ludwig's angina (autopsy), (2) cirrhosis of the liver (autopsy), (3) cardiorenal disease at 68 years of age, (4) "old age" at 75 years, (5) pneumonia at 44 years.

Although 44 of our patients survived more than thirteen years, no death attributable to cancer has occurred longer than twelve years after treatment.

Chart 3 depicts in another form the follow-up data on the groups of patients who survived five and ten years, respectively.

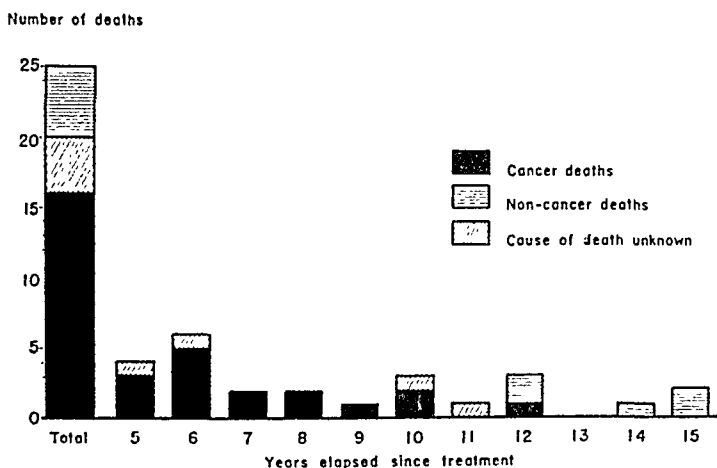


Chart 2.—Causes of mortality of 25 patients subsequent to five-year survival.

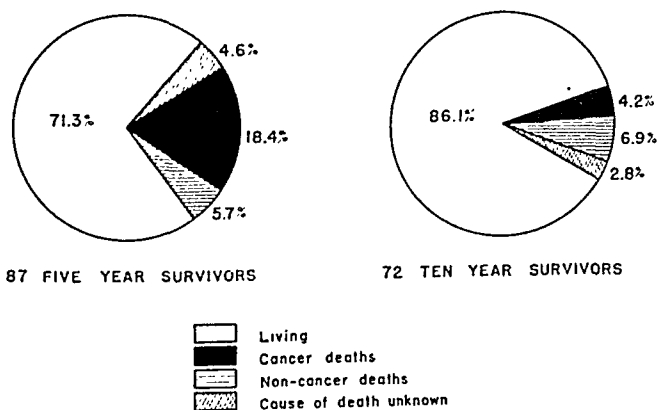


Chart 3.—Present status of five- and ten-year survivors.

SUMMARY

Seventy-eight per cent of 197 patients who survived five years lived 10 or more years after treatment.

Of 87 patients who survived five years after treatment, approximately 20 per cent subsequently died of cancer.

Seventy-two patients survived more than ten years and only 4 per cent of these died of cancer.

Forty-four patients lived thirteen years or more after treatment and none of these has died of cancer.

The complete follow-up records which made this study possible are due in large measure to the untiring efforts of Miss Etta Jones, to whom we acknowledge our indebtedness.

In a series of more than 800 cases of the radical vaginal operation our mortality rate was only about 3.9 per cent in comparison with the mortality of laparotomy, which, according to the statistics of the best men like Wertheim and Bonney, is as high as 15 per cent; in others even higher. For this reason we have felt that we should stick to the vaginal operation; all the more so because radiation treatment might take care of the glands. However, I begin to doubt whether this belief is correct after hearing what Dr. Taussig has said regarding the effect of radiation on carcinomatous glands.

Since the year 1916 I have systematically combined operation with radiation. I introduce radium immediately after the closing of the peritoneum in the radical vaginal operation, and radiate later with x-ray and radium. My results, which were first published at the International Congress in Stockholm, 1928, showed nearly 31 per cent of absolute cures resulting from the vaginal operation. Since then, I believe, my results have been even better.

I do not think that radiation on the one hand and operation on the other hand will be the final solution of the problem of cancer treatment. Since 1920 I have always advocated the so-called elective treatment, that is, I think that the method of treatment should be adapted to the general and local conditions in each case. I do operate on all operable cases if there is no contraindication against operation. My routine procedure is the radical vaginal operation; laparotomy is used exceptionally. In every case I introduce radium during the operation and use prophylactic radiation with radium and x-ray later. In all inoperable cases radiation is used and also in some operable cases, especially in the so-called borderline cases and when the condition of the patient is not good. With this selective treatment I have obtained between 38 per cent and 39 per cent absolute cures.

DR. CURTIS F. BURNAM, BALTIMORE, MD.—In general, the ten- or fifteen-year, and twenty-year cure rates, reported by Dr. Kimbrough, coincide with our own observations, which I reported in 1931. I recently saw a woman who had been treated in 1911 for cancer of the cervix by radiation, and who is still well. We have two other cases from that year.

My impression is that late recurrences are most likely to occur in those cases which originally were extensive, inoperable or borderline. The early cancers treated, that remain well for five years, usually stay well. It is, therefore, of interest in such reports as Dr. Kimbrough's to state the extent of the disease at the time of the original treatment.

Dr. Taussig, apparently, limits a removal of the pelvic lymph glands to cases in Groups 2 and 3. Undoubtedly, there is a greater incidence of lymph gland metastases in these advanced cases than in Group 1. Nevertheless, many of these do have metastases. The percentage of cures of early cases for different years, has varied from 100 per cent to 25 per cent, and this variation has been due almost exclusively to glandular metastases.

I must take exception to Dr. Taussig's statement that carcinoma involving the lymph glands of the pelvis cannot be eradicated by x-ray. I am quite sure that it can be in a considerable number of cases. It should be borne in mind, however, that there is a vast difference in ray sensitivity between different cases. I do not think this is due to the differences in histologic grading, but principally to differences in individual resistance of the patients concerned. So far as I know, we have never seen a case cured where there has been definite involvement of the glands above the pelvis in the retroperitoneal lumbar region.

A dosage of 5,000 r. units to the glands themselves, which Dr. Taussig says is the amount used in his cases, is a considerable one, and to give it safely, one should take from three to six weeks or even longer. My associates and myself, on the average, have used less milligram hours than most of the groups in this country and abroad. Nevertheless, in recent years, since we have begun using x-ray in conjunction with the radium, our tendency has been further to reduce the radium dosage.

In reviewing our records at Philadelphia General Hospital we find that 63 patients with microscopically proved carcinoma of the vulva have been admitted since 1922. Of these only five are still alive. These depressing results are doubtless due in part to our lack of Dr. Taussig's skill, and in part to the fact that in all of our patients the disease was well advanced. Twenty-six per cent of them lived less than one month after admission and 60 per cent were dead before six months had elapsed.

Of the 58 patients who died on our service, the neoplasm originated on the clitoris in 15, and on other portions of the vulva in 43. As a group, those with carcinoma of the clitoris were younger than those whose growth originated in other portions of the vulva. Squamous cell carcinoma was the predominant type and the majority of tumors were of the more radioresistant grades. There was one patient with sarcoma of the clitoris.

Thirteen of our patients were examined post mortem. In 4 of these, metastases, proved histologically, occurred in more distant situations than the inguinal nodes, the vagina, the rectum, or the bladder. The metastatic sites were as follows: lungs, pleura, liver, spleen, adrenals, kidneys, and nodules in the skin of the thigh. The occurrence of distant metastases, 31 per cent, in our series of vulvar carcinoma is strikingly like that found in our series of carcinoma of the cervix, 33 per cent.

Dr. Taussig's observations and the results he has secured indicate that extensive vulvectomy, with excision of all the regional nodes, and high voltage x-ray irradiation is the best treatment for patients in whom the disease is not too far advanced. For those in the latter stages of the disease, good palliative results can be secured, fairly consistently, with high voltage x-ray therapy.

DR. LEWIS C. SCHEFFEY, PHILADELPHIA, PA.—In a group of 101 patients treated with radiation from 1921 to 1928 on the Gynecologic Ward Service, Jefferson Medical College Hospital, we obtained a five-year salvage of 28 patients, or 27.7 per cent. Of these, 19 patients, or 18.8 per cent, were alive at the end of the ten-year period. This shows that 67 per cent of the 28 patients living for five years were salvaged for ten or more years. If we include 2 patients who died in the tenth year, but not of cancer, it would raise the ten-year survival rate of patients salvaged for five years to 75 per cent, corresponding approximately to Dr. Kimbrough's findings.

PROFESSOR LUDWIG ADLER, formerly of VIENNA.—Although I cannot give you exact figures since I was unable to bring my notes and papers from Vienna, I think that I may have a slightly higher percentage of cancer patients living after ten and fifteen years than Dr. Kimbrough's figures show. His investigations are important since it has been suggested that one should not take the five-year cures but only the ten-year cures as permanent. As the time following treatment increases, our patients become older and therefore, of course, their life expectancy decreases, with the result that more die from other causes. According to strict statistics deaths of all patients are considered as recurrences unless it is proved by post-mortem that the patient was free from a recurrence. Furthermore, the greatest part, about 80 per cent, I think in my cases it may be between 80 per cent and 90 per cent, of the women cured after five years are still living and free from cancer after ten years. For these reasons, therefore, I think the ten-year or the fifteen-year standard should not yet be adopted.

I would like to ask Dr. Taussig whether he has also made the observation that the involvement of the glands in cervical cancer does not always follow the anatomical route? One finds the glands in the pelvis uninvolved sometimes and yet in the same individual glands higher up will be found to be cancerous.

In this connection I should like to draw your attention to the fact that when the removed glands were carcinomatous, the patient was very rarely found to be free from recurrence after five years. Schauta's statistics proved this statement. This is one reason why the pupils of Schauta have stuck to the vaginal operation instead of adopting Wertheim's laparotomy.

MASCULINIZING TUMORS OF THE OVARY (ARRHENOBLASTOMA, ADRENAL OVARIAN TUMORS)*

WITH REPORT OF 6 ADDITIONAL CASES OF ARRHENOBLASTOMA

EMIL NOVAK, M.D., BALTIMORE, MD.

(From the Department of Gynecology, Johns Hopkins Medical School)

NOTWITHSTANDING their relative rarity, no group of ovarian neoplasms has excited more interest in recent years than those which have been shown to produce striking biologic effects upon the sex characters of the individual. That tumors of the ductless glands may bring about remarkable endocrinopathies had been known long before we began to speak of masculinizing or feminizing tumors of the ovary. Perhaps the first demonstration of this, on the basis of histologic and clinical rather than hormonal studies, was in the case of the pituitary. Although the growth hormone of the hypophysis has not yet been isolated, it has long been accepted, and on good scientific grounds, that overproduction of this hormone by adenomas involving the eosinophilic cells, the normal producers of the growth hormone, is the responsible factor in acromegaly and gigantism.

Since then an imposing group of syndromes has been shown to be due to tumors of one or other of the endocrine glands. Among such tumors the following may be mentioned as producing clinical syndromes which are rather clearly defined, viz., eosinophilic adenoma (already mentioned), basophilic adenoma and chromophobic adenoma of the pituitary, adenoma of the parathyroid, adenoma involving the islands of Langerhans in the pancreas, adenoma or carcinoma of the adrenal cortex, tumors of the adrenal medulla, and certain tumors of the gonads, male and female.

By contrast with the feminizing tumors which constitute the granulosa cell carcinoma group, the masculinizing variety, the arrhenoblastomas, are quite rare. The former make up approximately 10 per cent of all primary carcinomas of the ovary, and we have encountered, in our own material, and in that sent in from other clinics, no less than 68 instances. On the other hand, I have been able to collect from the entire literature only 45 cases of arrhenoblastoma, to which must be added the 6 cases included in the present report. In 1933 Sedlacek¹ was able to collect only 27, and in 1934 Kleine² added 8 more, including 4 of his own. Since then, additional cases have been reported by von Szathmary,³ Phelan,⁴ Gnassi,⁵ McLester,⁶ Baldwin and Gafford,⁷ Young and Te Linde,⁸ Schiller⁹ (also reported by Föderl), Schockaert,¹⁰ Miller¹¹ and Norris.¹² The case reported by Behrend and Levine¹³ in

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

NOTE: For lack of space, parts of this article and Figs. 2, 3, 4, 7, and 17 have been omitted but the complete paper may be had in the author's reprints.

DR. KIMBROUGH, JR. (closing).—For statistical reports I am still in favor of the five-year criterion but in using it we must bear in mind that subsequent to five-year survival approximately 20 per cent of patients will probably die of cancer.

DR. TAUSSIG (closing).—So far as cervix cancer is concerned there is no doubt that Group II cases are greatly benefited by the gland removal operation. I have now performed 86 such operations and have had but two deaths. That means that it is a safe operation so far as my individual experience is concerned. The mortality is much higher in the Bassett lymph gland removals for cancer of the vulva. It is easy to remove the pelvic glands in this way, and I am convinced that, while we are eliminating only two-thirds of the possibly carcinomatous glands of the pelvis, we have made a definite step in advance.

We have all seen the failure of heavy x-radiation to influence lymph gland metastasis. It is the experience of most x-ray men, that regression by this method is temporary, and that surgical removal of the glands is necessary for permanent cure.

On the question of endometriosis in lymph glands, it should be remembered that Wertheim, when he first began to perform his operation for cancer of the cervix, found in 48 out of 500 operations peculiar epithelial structures in the lymph glands. He thought they were carcinomatous at first but later finding them in noncancerous patients gave up the idea of classifying them as such. Recent work has shown that these are definitely of endometrial origin. I would like to suggest the following explanation of the marked frequency of lymph gland endometriosis in cervix cancer. It occurs in 9 per cent of such cases according to Wertheim's figures, and in my own series there was approximately the same percentage. In recent reports of French operators there has been a similar high incidence of lymph gland endometriosis. My theory is that since the cervix is partly or completely blocked by the carcinoma, the endometrial particles at menstruation cannot gain an exit through the cervical canal. Above the point of carcinoma blockade there are open lymph channels and through these the particles of endometrium are readily carried out through the lymphatics to the tributary glands.

Clinical Features.—Arrhenoblastoma of the ovary occurs most frequently in relatively young patients, the decade between 20 and 30 showing the largest incidence. The youngest patient, so far as I can find, was 15. It is relatively rare beyond the menopause, though rather surprisingly, all 4 of the group recently reported by Kleine² were beyond 50, and Meyer has described such a tumor in a patient of 66.

The clinical course of these patients is characteristically divisible into two phases. There is first a stage of defeminization in which certain typical feminine characteristics are subtracted from the patient, and this is followed, with possible overlapping, by a stage of masculinization, in which certain positive masculine characteristics are added. Chief among the defeminization symptoms are amenorrhea, atrophy of the breasts, and loss of the subcutaneous fatty de-

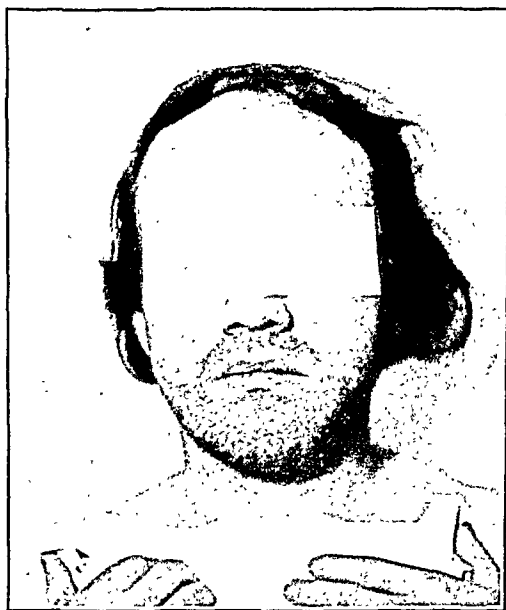


Fig. 1.—Extreme facial hirsutism in a case of female pseudohermaphroditism due to adrenal cortical hyperplasia, as was later demonstrated by autopsy.

posits which are responsible for the rounding of the feminine figure. Of the masculinization signs, the chief are hypertrophy of the clitoris, hirsutism, and deepening of the voice.

The first symptom noted by most patients is amenorrhea, which may come on abruptly. Regression of the mammary glands soon occurs. Changes in body contour may not be conspicuous and are often not noticed by the patient herself or at least not until hirsutism has developed. The aberrant growth of hair, in my experience, does not usually reach the degree observed with adrenal cortical lesions. For example, Fig. 1 shows the very heavy facial growth of hair in a patient with bilateral cortical hyperplasia, as proved by operation, though no lesion of the ovary was present. In arrhenoblastoma patients the facial hirsutism may be sufficiently heavy to compel daily shaving. In addition there may be extensive hirsutism of both the upper and lower extremities, with perhaps also much hair on the

1936 I am omitting, as both the clinical and pathologic descriptions, as well as the photomicrograph of its histologic appearance, make it seem extremely doubtful.

* * *

Gross Pathology.—These tumors, as encountered at operation, are usually of moderate size, and may be very small, though in a number of reported instances they have reached large proportions, even to the size of a man's head. Characteristically, especially when of small size, they are solid tumors, though they not infrequently exhibit one or more cystic areas, and in the larger tumors the cysts may be of large size. The color and consistency are variable, depending upon their widely differing histologic structure. They may be grayish, with frequently areas of definitely yellowish hue, but in some, the color of the cut surface is bluish, purplish, or reddish-blue. The consistency may be quite firm in some cases, but degenerative changes are common, as is hemorrhage. In some reported instances, especially those of the testicular adenoma type, the tumors have been described as of elastic feel, like normal testicular tissue.

Microscopic Examination.—A description of the microscopic characteristics of arrhenoblastoma is not easy, because of the extreme variations which may be encountered in different cases, and in different parts of the same tumor. At one extreme is the highly differentiated variety corresponding to the testicular adenoma described by Pick in 1905, and characterized by a very definite tubular structure, reproducing more or less perfectly the structure of normal testicular tubules. At the other extreme is the very undifferentiated variety which at first sight may be considered a typical sarcoma, and in which only very careful study of many blocks may reveal the presence of sex-cordlike structures, or imperfect tubules, or lipoid-containing cells corresponding to interstitial cells. Finally, in the group designated by Meyer as the intermediate, one finds usually a varying number and distribution of definite tubular structures, interstitial cells, and of cell columns arranged in rather zigzag fashion, quite like the sex cords seen in the early development of the gonads.

* * *

Malignancy.—While arrhenoblastoma is properly classified as a malignant tumor, there is no doubt that its degree of malignancy, like that of granulosa cell carcinoma, is much less than that of ovarian cancer in general. On the other hand, it must be remembered that many of the reports of this newly-recognized and interesting tumor type have been made very soon after their observation, so that one cannot always be certain whether or not later recurrence had occurred. Even so, there are already available sufficient reports to indicate that in some cases the tumor may exhibit highly malignant characteristics. The case previously reported from this laboratory (Novak and Long) terminated fatally, as did also 2 cases reported by Meyer. Moreover, recurrence of the tumor occurred in the case reported by Taylor, Wolfermann and Krock, that of Kleinhans, and also in the recent case of von Szathmary. On the other hand, in the great majority of cases reported in the literature, the patient has remained well after removal of the ovary, in spite of the fact that the operation performed was most frequently of conservative nature, usually unilateral salpingo-oophorectomy. It is too soon as yet to offer any worthwhile figures as to the frequency of recurrence and the degree of malignancy, but on the basis of the literature to date there is ample justification for the statement that the degree of malignancy of these tumors as a class is far lower than that of ovarian cancer in general. The same statement can be made concerning granulosa cell cancer and dysgerminoma.

about 104.5° F. for a number of days. The following month, however, the period occurred, and has been entirely normal in character and rhythm since that time.

Another rather prompt evidence of refeminization is the development of the breasts, so that within a few months they are often quite normal. The same thing applies to the general body weight and the body contour.

When we come to the positive manifestations of masculinization, however, we find that these disappear much more slowly than those of defeminization, and often incompletely. When hypertrophy of the clitoris is very marked, the organ may remain abnormally large, so that amputation may be called for. In the milder cases, however, regression is definite though sometimes rather slow. The disappearance of the abnormal hair growth is often a rather slow process, requiring many months, though in many reported cases, as in my Case 1, the recession has been much more rapid.

In a number of the reported cases, pregnancy has been observed to occur after removal of the tumor. One of my patients (Case 2) has had two pregnancies in the two years since operation, though she miscarried each time. Another (Case 4) gave birth to a living full-term child fourteen months after operation. Sedlaczek, in the 27 cases collected by him, found that 5 patients had become pregnant, 2 within two years following operation.

CASE REPORTS OF ARRHENOBLASTOMA

CASE 1.—This patient, aged 35, was referred to me on October 20, 1937, by Dr. J. G. Howell, of Catonsville, Md. She had been quite normal until November of 1936, when menstruation, which had previously recurred at regular four-weekly intervals, had ceased abruptly. There had been one full-term pregnancy seven years previously. During the past ten or eleven months she had developed a considerable growth of rather long downy hair on the upper lip, cheeks, and chin. The legs and arms had been somewhat hairy since puberty, but the hair growth on the extremities had recently become much heavier. The breasts had become much smaller and flatter, and since June the patient had been suffering, as she said, with a persistent "laryngitis" which made her voice rough and much deeper than formerly. She had herself noticed an enlargement of the clitoris. Recently there had been occasional aching pain in the right lower abdomen. There had been no impairment of libido.

The examination showed the weight of the patient to be 119 pounds, and her height 5 feet, 5 inches. The contour of the figure was rather angular, and the breasts were very flat (Fig. 2). The hairy growth was as above described, with also a heavy growth covering the lower abdomen and with a distinctly masculine crines.

Pelvic examination showed moderate but definite hypertrophy of the clitoris, which measured 4½ cm. in length, with a much thickened body, and a glans something over 1 cm. in diameter. The uterus was rather small and pushed slightly to the left by an ovoid, freely movable mass of rather elastic feel, about the size of a lemon, evidently a small tumor of the right ovary. The left adnexa were normal. In view of the history and the pelvic findings, a presumptive diagnosis of arrhenoblastoma was made.

Operation, on Oct. 27, 1937, revealed the tumor of the right ovary to be about the expected size, with smooth external surface, and of elastic feel, so that externally it resembled a cyst, though when it was later cut into, it proved to be an entirely solid growth, as will be described below. The left ovary was below the average size, with a whitish, opaque, and rather corrugated surface, and with no

abdomen and chest. In some cases, on the other hand, the hirsutism may be very moderate, and the pubic hair may retain its characteristically feminine horizontal upper border, as in my Case 1.

At this point I may again emphasize that hirsutism in itself is not necessarily an evidence of masculinization. There are many otherwise typically feminine patients, who menstruate normally, and bear many children, and whose physical and psychologic characters are otherwise perfectly feminine, who nevertheless show extensive hirsutism, as every gynecologist knows. While the adrenal is undoubtedly concerned with both hair distribution and sex characteristics, there is no evidence that the two functions are combined in the same cells or group of cells. As a matter of fact, there is reason to believe that the frequent association of hirsutism with more characteristic masculinization phenomena may be incidental, as a result of associated involvement of two separate cell types or groups.

The loss of the typically rounded female contour may be pronounced or it may be only slightly marked, and the duration of the tumor as well as the degree of its secretory activity, would seem to explain these individual variations. Loss of body weight is a common observation, as would be expected from the decrease of subcutaneous adipose tissue.

The changes in the patient's voice are often very noticeable, she herself often attributing this to a persistent "cold" or laryngitis, as in my Case 1. A normally soft, high-pitched feminine voice may be changed to a baritone or even to a basso, with often hoarseness or roughening of the voice. These vocal changes are due to lengthening of the vocal cords, while in marked cases there is overgrowth of the laryngeal cartilages, with the development of a prominent "Adam's Apple."

With reference to the hypertrophy of the clitoris, here again there are marked individual variations. In some cases it is only slight, in others the clitoris may assume the proportions of a miniature penis.

* * *

Effects of Tumor Removal on Symptoms.—The crucial clinical test in the substantiation of a diagnosis of arrhenoblastoma is the regression of the abnormal masculinization symptoms after the removal of the tumor. Though this regression may not be complete in every case, it is usually striking in undoubted cases of arrhenoblastoma. The return of menstruation is the first manifestation of returning femininity, and in general the symptoms disappear in an order the reverse of that of their appearance. Almost without exception menstruation has reappeared about twenty-eight days after the removal of the tumor. One of the few exceptions is my Case 1, though here the failure of the period to occur at the end of the first postoperative month is readily explained by the fact that the patient was extremely ill at that time as a result of a pelvic abscess, with a temperature of

tures closely resembling the rete tubules of the normal ovary (Fig. 3). Sections from all parts of the tumor showed all stages of transition from sarcomalike areas, to areas in which there was a definitely cordlike arrangement of the cells, to still others with occasional well-defined tubules, and finally areas with a very conspicuously tubular pattern. The cells in the compact areas were round or spindle-shaped, with deep-staining nuclei of various shapes and sizes. The lining epithelium of the tubules varied somewhat, though for the most part it was either cuboidal or columnar, with ovoid, granular nuclei. A few mitotic figures were seen. In some sections one found columns or alveoli of large, eosin-staining polyhedral cells, which morphologically resembled the interstitial cells of the testis, and this impression was given support by the fact that abundant lipoid was demonstrable in these cells by differential staining.

CASE 2.—H. D., a young woman of 24 years, had been quite normal until twenty months before I first saw her, on Aug. 19, 1935, through the kindness of Dr. W. C. Caudill, of Pearisburg, Va. She had been married six years, and had had one nor-



Fig. 6.

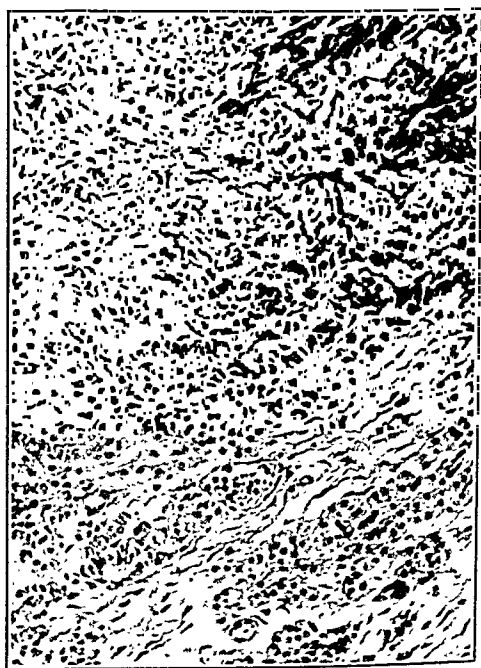


Fig. 8.

Fig. 6.—Aggregations of cells which morphologically, and in their lipoidal staining, exactly resemble the interstitial cells of Leydig of the normal testis.

Fig. 8.—Microscopic appearance of tumor in Case 2. Note the characteristic cords of cells, with nuclei perpendicular to the long axis of the cords, and also the islands of interstitial cells to the left.

mal childbirth five years previously. There had been complete amenorrhea for two years before I saw her, though there had been a rather profuse whitish leucorrhea. About a year ago a growth of hair appeared on her face, involving the upper lip, chin, and both cheeks, with also a heavy hair growth on the upper and lower extremities and on the abdomen. The breasts had become small and flaccid, and the voice had become markedly deeper.

The patient, on examination, was 5 feet, 4 inches tall, and weighed 134 pounds. The general build was normal, though there was a tendency to angularity. There was a moderately heavy growth of dark hair on the upper lip and cheek, with much less on the chin, and a heavy growth on both upper and lower extremities. The pubic hair was of the masculine type, extending in the midline to the umbilicus. There was no enlargement of the thyroid, and both breasts were small and flaccid, with no secretion.

external evidence of follicular activity. A right salpingo-oophorectomy was done and the appendix was removed. Both adrenal glands were carefully palpated, showing no appreciable enlargement and no palpable nodules.

The convalescence of the patient was marred by the development of a late pelvic abscess, presumably due to infection of a hematocele, and she ran a febrile course for many days before the abscess was evacuated by pelvic puncture on November 8. During this period the patient was quite weak and prostrated, though the later recovery was uneventful.

Postoperative Course.—Probably because of the patient's poor condition for some weeks after operation, the first menstrual period did not occur until January 18, just about twelve weeks after operation, but since then it has recurred regularly at intervals of about four weeks, the duration being four or five days, and the amount moderately free. The breasts have returned to their original size, the facial hair has practically entirely disappeared, and the hair on the extremities has become much less in amount. Especially striking has been the change in voice, which now again is high-pitched instead of having a rough baritone quality. The clitoris is

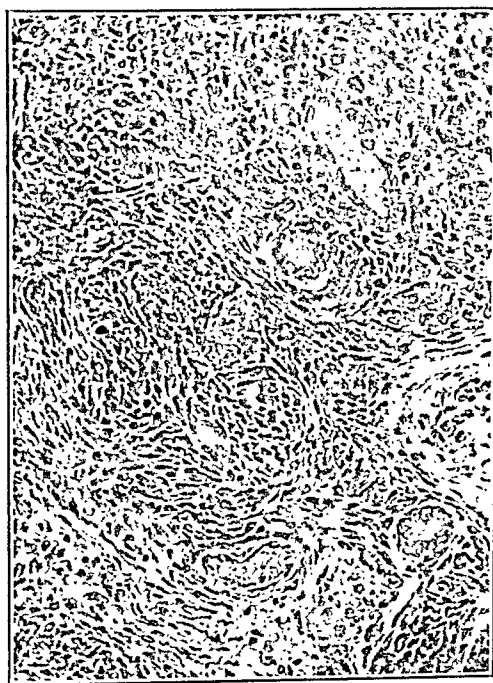


Fig. 5.—Another area in Case 1, showing definite tubules, with a picture quite characteristic of the intermediate type of arrhenoblastoma. This is the prevailing pattern in Case 1.

still above average size, though noticeably smaller than before operation. A pelvic examination made very recently, seven months after operation, shows no indication of recurrence.

Report of Pathologic Examination.—The specimen was a globular mass, measuring 5.5 cm. in diameter, with a normal tube appended. The external surface was quite smooth, and on section the tumor proper was seen to be surrounded by a thin cortical layer of what looked like normal ovarian tissue. The tumor itself presented in most places a reddish-purple, hemorrhagic appearance, with other areas which were grayish and granular, and with a yellowish tinge here and there.

The microscopic examination, like the gross, showed the tumor to be obviously of medullary origin, the cortex being flattened out about the tumor, and showing a few Graafian follicles in various stages of maturation, together with a rather large corpus albicans. Beneath the cortical layer the tumor itself presented a rather sharp though slightly lobulated outline. Its central margin extended well toward the hilum, where thin strands of cells, resembling sex cords, passed into the region of the rete ovarii. In this deeper portion the tumor itself showed some tubular struc-

Microscopically, as in most cases of arrhenoblastoma, wide variations in histologic appearance were seen in different parts of the tumor. In some the structure was quite compact, in others of loose texture, with areas of even myxomatous appearance. In the more solid areas, one could see the characteristic cordlike arrangement of the cells, while in others they formed more substantial columns. The cells were round or spindle, with chromatin-rich nuclei of differing shape. In the peripheral parts of the tumor a frankly tubular pattern was seen, the tubules being lined by epithelium which in some places was very low, in others rather tall and peglike. Islands of cells which histologically resembled Leydig cells were seen here and there, especially in the distinctly tubular portions.

Postoperative Course.—A recent letter from Dr. Giordano informs me that "menstruation was re-established, but the voice still remains masculine and the patient still has to shave regularly. There has been no evidence of recurrence and the patient is still perfectly well" (about three and one-half years after operation).

CASE 4.—On Nov. 9, 1936, Dr. J. P. Lovett of Olney, Texas, kindly sent me slides from a tumor of the left ovary which had just been removed from a girl of 17 years,



Fig. 9.



Fig. 10.

Fig. 9.—Microscopic picture in Case 3, showing characteristic sex-cordlike pattern.
 Fig. 10.—Tubular pattern in parts of tumor from Case 3.

and later was good enough to send me a portion of the tumor for further study. I am indebted to him for permission to include this case in the present report. This patient had begun to menstruate at the age of 13, and the periods had been normal until the age of 15, when they became scanty and soon ceased entirely. There had been complete amenorrhea for fifteen months before operation. Marked facial acne was noted. "She developed the contour of a male, the breasts retrogressed, the clitoris became markedly hypertrophic, and the voice became much deeper."

Report of Pathologic Examination.—The tissue consisted only of several small portions of the original tumor, so that no gross description is possible. Microscopically the tumor was composed of strands and masses of rather small cells, with considerable areas of intervening loose connective tissue. The blood vessels were large and numerous. The tumor cells were round or oval, with dark-staining nuclei which varied much in size and shape. In some areas, however, the cells were spindle-shaped. Here and there one found a tendency toward an imperfect tubular pattern,

The pelvic examination disclosed a marital outlet, without relaxation. The vaginal mucosa was reddened and congested, with slight leucorrheal discharge. The cervix was only slightly lacerated, and pointed downward and forward. The uterus was small, moderately retroflexed and freely movable. In the left side of the pelvis could be felt an ovoid, freely movable mass about the size of a lemon. It was of rather elastic feel, and was obviously a neoplasm of the left ovary. The right adnexa seemed normal.

A presumptive diagnosis of arrhenoblastoma was made, but as circumstances made it impossible for the patient to remain in Baltimore, she returned to her home and was operated upon shortly afterward (September 3) by Dr. Albert H. Hoge, of Bluefield, West Virginia, who was good enough to send me the tumor which was removed.

Report of Pathologic Examination.—The specimen consisted of a tumor measuring 9 by 8 by 6 cm. The surface was smooth and of bluish white color. Attached to one side was a normal Fallopian tube. The cut section of the tumor showed it to contain many small cystic cavities, some containing a clear fluid, others a mucoid material, while other areas were solid, and of puttylike appearance and consistency.

Microscopically this tumor, like that in Case 1, was apparently of medullary origin, well-circumscribed, and moderately lobulated. It was of interest, however, that in this as in other tumors of this type which I have examined, arrhenoblastomatous elements occurred outside the tumor proper, which was surrounded by a fairly thick connective tissue capsule. A thin enveloping shell of ovarian cortex, showing a number of atretic follicles, could be made out in several areas.

The structure of the tumor was quite cellular and sarcomalike in some places, though even here there was a rather characteristic choppiness of pattern due to the tendency of the cells to arrange themselves in short anastomotic columns. In other parts this cordlike tendency was much more outspoken. These cords were made up of a single or double row of cells whose darkly staining nuclei were placed perpendicularly to the long axis of the column. Between these were collections of much larger, polyhedral cells, with eosin-staining cytoplasm and small round nuclei, which resembled interstitial cells. The cells in the more compact areas were round or fusiform, with heavily staining nuclei of irregular shape and size. A moderate number of mitoses were seen. Large areas of the tumor showed extensive coagulation necrosis.

Postoperative Course.—This could best be summarized in the patient's own words, as expressed in a letter of recent date. "My menstruation returned exactly one month from the day I was operated upon, and has been very regular since. I have been pregnant twice since, but lost both at two months or about that time. The hair has completely disappeared, and there has been a great improvement in my voice, but it is not back to normal yet."

CASE 3.—For the privilege of including this case in my series I am indebted to Dr. A. Giordano, of South Bend, Indiana, who was good enough also to send me a generous portion of the tumor. The patient was a girl of 22 years who had previously been normal, but who one year before operation ceased menstruating. The breasts became very small, the voice became deeper and rather hoarse, and she developed a heavy facial growth of hair, as well as marked hirsutism on the extremities and abdomen. At this time examination by the family physician disclosed an abdominal tumor, which at operation (Sept. 28, 1934) proved to be of ovarian origin.

Pathologic Examination.—The specimen consisted of a slice of tumor tissue, measuring 9 cm. in diameter (presumably the diameter of the tumor) and 3 cm. in thickness. The external surface was of grayish-wrinkled appearance, in places almost resembling pigskin. The cut surface showed numerous cystic spaces, varying from a few millimeters to 3 cm. in diameter. The intercystic tissue was of grayish color, though in one quadrant it was yellowish and firm, with only a few tiny cystic areas.

consistency was like that of fixed brain tissue. The surface showed lobulations of about 1 to 2 cm. in diameter.

Microscopically, the tumor is made up dominantly of an adenoma-like tissue, showing large numbers of wide tubular lumina arranged in groups or islands set in a sparse connective tissue substrate. The closely packed tubules are lined with a single layer of large oval or low columnar epithelium, with rather large nuclei and an occasional mitotic figure. The tubules bear a striking resemblance to seminiferous tubules, and in places the lining epithelial cells are not unlike the Sertoli cells of the testis. There is some shedding of the lining epithelium into the lumen of some of the tubules. In a number of areas the tubules are lined by a much lower epithelium, with more abundant interlobular connective tissue, such areas being strongly reminiscent of the rete testis. A few of the tubules are dilated and cystic. No cells which morphologically resemble Leydig cells can be seen in the interstitial tissue.

Postoperative Course.—The patient, according to a recent report, has remained perfectly well since operation, and menstruation has again become normal in character and amount. (Letter from Dr. Hagebusch Feb. 18, 1938, ten months after operation.)

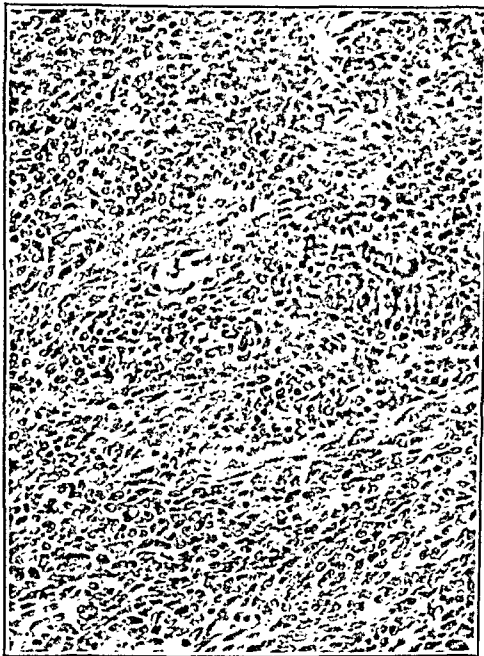


Fig. 13.—Microscopic appearance in Case 6, with rather broad cords of cells shown in this field, though in most parts the tumor cannot be differentiated from sarcoma.

CASE 6.—For the privilege of adding this case to my series I am indebted to Dr. R. L. Gench, Fort Scott, Kansas, and Dr. Ferdinand C. Helwig, of Kansas City, Missouri. The patient, 34 years of age, had had complete amenorrhea for seven months, and three or four months before operation she developed a heavy growth of facial hair, especially on the chin, as well as hirsutism of the extremities and abdomen, where the hair extended from the pubes in a triangular fashion to the umbilicus. She had been obliged to shave regularly. It has not been possible to secure any information as to any changes in the breasts, clitoris, or voice. A unilateral ovarian tumor was removed at operation by Dr. Gench on April 25, 1937.

Report of Pathologic Examination.—The specimen which Dr. Helwig kindly sent me was a rather globular tumor measuring 10 by 9 by 6 cm. The surface was slightly irregular, like that of the normal ovary. The tumor was of even consistency except at one portion, where there was a soft spongy, easily compressible area about 2 cm. in diameter. On section the tumor showed a rather cream-colored slightly granular surface, though in many places the tissue felt gummy, and in the one area above

the lumina being of small caliber, but the characteristic cordlike arrangement was very pronounced, even where there was no evidence of tubules. An occasional mitosis was seen, and small collections of cells suggestive of Leydig cells were also encountered in some parts of the sections.

Postoperative Course.—Three months after operation Dr. Lovett wrote me that the patient had been married two months previously, and was enjoying perfect health, having already gained 15 pounds. The figure had again become rounded, and the abnormal hair growth on both the face and the rest of the body had practically disappeared. The voice was still a trifle husky, though "the patient humorously remarked that she could again sing." The breasts had become larger than those of the average female of her age. The facial acne had disappeared. "The most remarkable feature of this patient," wrote Dr. Lovett, "had been the hypertrophy of the clitoris, which had regressed in size so that it is now not much larger than the average." There was no sign of recurrence of the tumor. More recently Dr. Lovett has informed me that the patient gave birth to a normal full-term child fourteen months after operation.

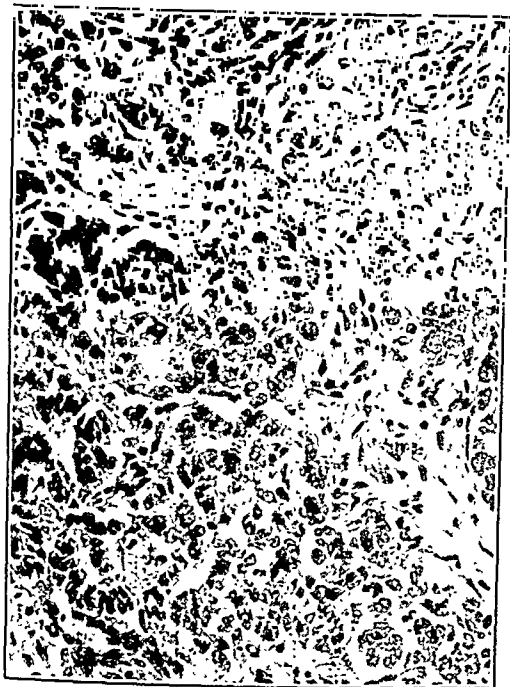


Fig. 11.



Fig. 12.

Fig. 11.—Microscopic appearance of tumor in Case 4.

Fig. 12.—Microscopic picture in Case 5, showing a highly tubular pattern (testicular adenoma) not unlike that of seminiferous tubules, though in many parts (lower right) the tubules are reminiscent of the rete testis. No interstitial cells could be demonstrated in this case.

CASE 5.—For the privilege of studying this case, and including it in this report, I am indebted to Dr. Omer E. Hagebusch and Dr. T. J. Kemp, of St. Louis, Missouri. The patient, aged 40 years, gave as her chief complaints pelvic discomfort and extreme scantiness of menstruation for a number of months. There was no evidence of masculinization manifestations, such as abnormal hair growth, hypertrophy of the clitoris, or deepening of the voice. The patient had had one pregnancy, terminating in early miscarriage in 1931. Examination by Dr. Kemp disclosed a tumor mass in the abdomen, and at operation (Dr. Kemp) on April 23, 1937, a large tumor of the right ovary was revealed. It measured 10 cm. in diameter, and was perfectly smooth and quite symmetrical. The right adnexa were removed. The tumor, on being opened, was found to contain lobulated masses of a brainlike tumor substance attached only over a limited area to the capsule, which was about 2 mm. thick.

Report of Pathologic Examination.—The tissue sent to me by Dr. Hagebusch was a part of the tumor, measuring about 4 cm. in its greatest diameter. The color and

The most perfect clinical simulation of arrhenoblastoma, however, is seen in the case of certain rare ovarian tumors which are composed of adrenal tissue. In spite of the infrequency of these neoplasms, it so happens that within little more than a year I have received for examination slides or tissue from 3 instances of this interesting tumor type. These came from Dr. A. Rottino, of St. Vincent's Hospital, New York, Drs. E. Perry McCullagh and Allen Graham, of the Cleveland Clinic, and Drs. H. J. Schattenberg and Hilliard Miller, of Tulane University. While all these cases will later be more fully reported by the observers themselves, they have kindly permitted me to make preliminary brief mention of them in this paper. A glance at the histories will reveal how perfectly these mimic the symptomatology of arrhenoblastoma.

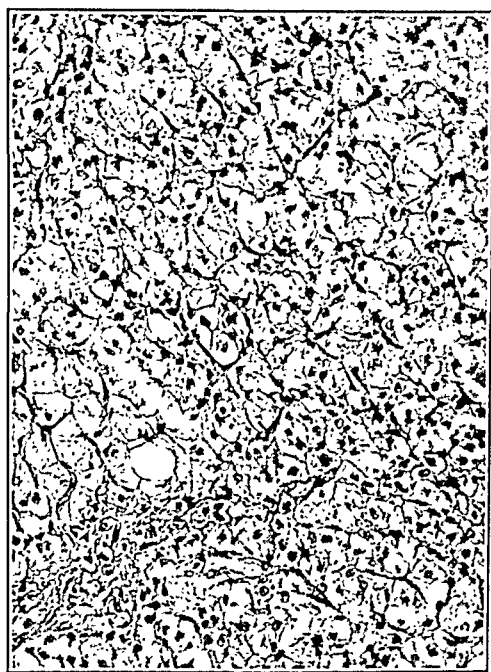


Fig. 14.—Typical adrenal tissue making up ovarian tumor in Case 7.

CASE REPORTS OF ADRENAL TUMORS OF THE OVARY

CASE 1.—(Dr. Rottino.) The patient, aged 24 years, had menstruated normally until the age of 20, when the menses abruptly ceased. She had borne one child six and one-half years before operation. Marked facial hirsutism developed, requiring daily shaving, and there was also a heavy growth over the chest, abdomen, and both upper and lower extremities. There was enlargement of the clitoris, and the voice was slightly husky. At operation (June, 1937), the adrenals were carefully explored and found normal. The right ovary was found to be twice normal in size, and on section a sharply circumscribed orange-colored, roughly spherical nodule was revealed, measuring 3 by $2\frac{1}{2}$ cm. in diameter. It occupied chiefly the medullary portion of the ovary, the cortex being thinned out to form a sort of capsule about the tumor. Microscopically, the tumor showed the typical structure of adrenal tissue, with not the slightest histologic resemblance to arrhenoblastoma. Dr. Rottino states that since the operation "the menstrual periods have returned, the patient has lost her husky voice, she shaves less frequently, and the hairs have become finer in texture and can be easily pulled out."

described, quite spongy. In the center of the tumor there was a whitish area of rather firm fibrous consistency. A few fairly large blood vessels were seen, but there were no cystic areas.

Microscopically, all the sections from many blocks showed in the main what looks like a mixed cell sarcoma. In many places, however, the sarcoma areas were traversed by bundles of spindle cells resembling unstriated muscle. The cells of the sarcoma areas were round or spindle in shape, with large, heavily-staining nuclei. A moderate number of mitoses were seen. In several areas of some of the sections there was a suggestion of tubular pattern, the occasional tubules being lined by a single layer of epithelium. Scattered here and there were larger cells with eosin-staining cytoplasm morphologically resembling interstitial cells. The cordlike arrangement of the cells in some places, with the occasional occurrence of tiny imperfect tubules, would seem to justify the classification of the tumor as a highly indifferntiated sarcomalike variety of arrhenoblastoma.

Postoperative Course.—Dr. Gench reported, on Feb. 12, 1938, that it had not been possible to induce the patient to return for re-examination. She wrote, however, that menstruation returned twenty-eight days after operation, and that she was perfectly well (ten months after operation).

DIAGNOSIS OF ARRHENOBLASTOMA

The appearance, in a previously normal woman, of such defeminization and masculinization phenomena as have been detailed above, together with the presence of a tumor of the ovary, warrants a strong suspicion of arrhenoblastoma. The endocrinopathy which most frequently calls for differentiation is that associated with cortical lesions of the adrenal, since these produce a clinical picture almost exactly like that of arrhenoblastoma. Usually, however, the symptoms are more gradual in development, and no ovarian tumor is palpable. Even though an ovarian neoplasm is present, together with masculinization symptoms, the diagnosis of arrhenoblastoma cannot be considered absolute. I have operated upon a number of such cases in which the ovarian tumor proved to be a simple cystadenoma, with not the slightest trace of arrhenoblastomatous elements even on very complete microscopic study. In such cases, as might have been expected, there was no regression of symptoms after the removal of the tumor, whose existence was simply coincidental in a patient suffering with an adrenal endocrinopathy. I am here discussing those cases, and they are numerous, in which no tumor of the adrenal is palpable, and in which none can be demonstrated by such diagnostic adjuvants as pyelography, pneumoperitoneum, etc.

In this connection I may mention an interesting specimen for which I am indebted to Dr. Victor Bergstrom, of Binghamton, N. Y. The patient, aged 22 years, had had scanty menstruation for three months, and was said to have developed a hoarse voice, marked masculine hirsutism, and atrophy of the breasts. There was no hypertrophy of the clitoris. At operation a large tumor of the ovary was found. Histologic study of many blocks from all parts of the tumor failed to show any evidence of arrhenoblastoma, and, from the presence of areas of cartilage and other alien tissues, it seemed that the tumor should be classified as a teratoma. No chorioepitheliomatous elements could be demonstrated. In response to a recent inquiry Dr. Bergstrom informs me that there has been no change in the patient's characteristics since operation, confirming our view that the masculinization changes were due, not to the ovarian tumor, but to some other endocrine factor, probably of adrenal cortical origin.

Report of Pathologic Examination.—Specimen consisted of the major portion of the right and left ovaries. The left ovary weighed 25 gm. and measured 5 by 2.8 by 2.6 cm. It was fairly firm and the external surface was rather irregular due to a few bulging cystic areas along the outer rim. On section, there was an outer compressed rim of ovarian tissue, measuring 4 mm. in thickness. There were a number of follicular cysts in this area. These contained blood-tinged fluid. The major portion of the ovary was occupied by a fairly discrete, firm, oval-shaped mass of tissue. There was a considerable amount of hyalinization present in this tissue and the remainder was composed of moderately firm, yellow, granular tissue. The right ovary weighed 10 gm. and measured 4 by 3 by 2.2 cm. On section, there were a number of follicular cysts present, but there was no tissue resembling that found in the left ovary.

“Microscopically, the right ovary shows numerous, simple, follicular cysts in the cortex and one, fairly large cyst, lined by a single layer of columnar epithelial cells, resting on a dense layer of collagenous, fibrous tissue. There are no other unusual features about the right ovary. Sections of the left ovary show several, small, simple follicular cysts in the cortex, and several primordial follicles. In the central portions of the ovary, there is a large area of tumor tissue consisting of small alveoli containing large, polygonal cells, which have a large amount of vacuolated cytoplasm and relatively small round or oval, deeply staining nuclei. The cytoplasm is finely reticulated and somewhat granular in the less vacuolated cells. The alveoli are separated by a well vascularized, delicate, trabecular tissue stroma. There are numerous areas of dense, hyalinized scar tissue scattered through the tumor. There is no distinct gland formation or tubular formation in any of the sections. There is no distinct capsule between the tumor area and the overlying ovarian cortex.” (Dr. Graham’s note.)

Postoperative Course.—A letter from the patient to Dr. McCullagh nearly three years after the operation stated that her general health was good, except that she was still rather nervous and tired easily. The hair growth was not much changed, and the weight was 134 pounds. Not a single menstrual period had been skipped since operation.

CASE 3.—(Drs. Schattenberg and Miller.) This patient, aged 27 years, had, eight or nine months previously, developed hirsutism, enlargement of the clitoris to 3 or 4 times the normal size, and a marked deepening of the voice. There had been amenorrhea for one year, and the breasts were flat. Clinically, it was thought that she had an arrhenoblastoma of the ovary. A small tumor of the right ovary was actually found at the operation performed by Dr. Miller (Feb. 18, 1938). It was 2 cm. in diameter, entirely within the substance of the ovary, and of golden yellow color. Microscopically the sections showed the tumor to consist of what was apparently typical adrenal tissue, identical in appearance with the two preceding cases. There is not the slightest resemblance to any type of arrhenoblastoma. As to the post-operative course, Dr. Schattenberg informs me that menstruation returned on April 15, about two months after operation, and that there has been definite retrogression of the other symptoms, though only a short time has elapsed since the operation.

Here, then, we have to deal with three adrenal blastomas of the ovary which produced masculinization symptoms identical with those of arrhenoblastoma, and, as with the latter, there was a striking regression of the abnormal manifestations after removal of the tumor. And yet none of these tumors histologically could be mistaken for arrhenoblastoma. The fact that adrenal tumors with this masculinizing capacity can occur in the ovary, and that they produce symptoms similar to arrhenoblastoma, must be taken as evidence of both the embryologic and biologic kinship of the two anlagen.

The whole question of adrenal tumors of the ovary, and particularly of their relationship with the so-called luteomas, is still in a confused state. I have in previous papers expressed doubt that the

CASE 2.—(Drs. McCullagh and Graham.) The patient, aged 37 years, had begun to menstruate at 14, the periods always being irregular, with intervals of from two to six months, the flow being sometimes scanty, sometimes profuse. During 1931 there were 12 periods, some 2 weeks apart and quite profuse. Between 1931 and 1934, when she came under observation, there had been only 5 menstrual periods.

The breasts were well developed and not tender. There was moderate hirsutism of the face, upper lip, cheeks, chin, breasts, abdomen, and extremities. The voice was deep, although definitely feminine. The clitoris was markedly hypertrophied, and the labia normal. The cervix was soft and boggy, and the adnexa free from tenderness or masses. The fundus could not be well outlined because of the obesity, but was, apparently, in good position. Her height was 63 inches, and her weight 160 pounds. The blood pressure was 130 systolic and 90 diastolic.

The blood count showed 4,980,000 red cells and 97 per cent hemoglobin. The urinalysis, fasting blood sugar, and blood Wassermann were normal. An x-ray of the sella and the visual fields revealed no abnormality. X-rays of the kidneys, ureters, and bladder were done, because she had chronic left lumbar pain, and showed no abnormality. Bilateral pyelograms were normal. The basal metabolic rate was minus 7 per cent.

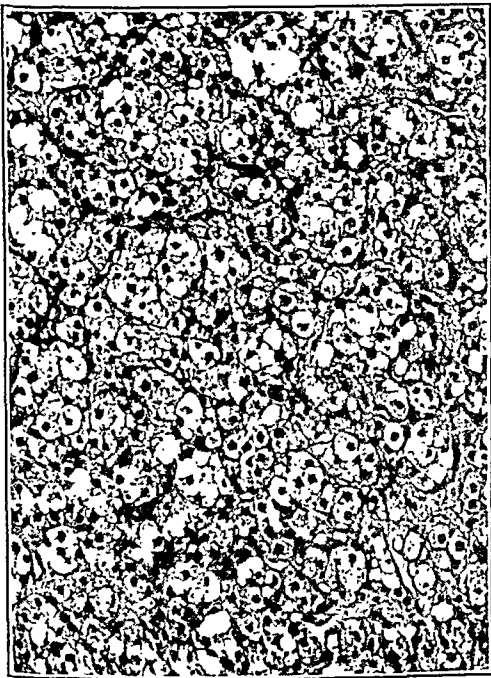


Fig. 15.

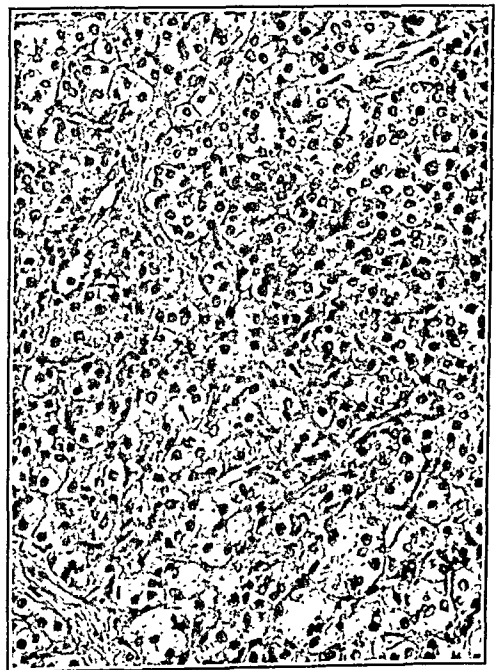


Fig. 16.

Fig. 15.—Microscopic appearance of adrenal ovarian tumor in Case 8.

Fig. 16.—Microscopic appearance of adrenal ovarian tumor in Case 9.

At intervals of a week 2 estrin assays were done by the Kurzrok method, and showed less than 4 rat units in each of two twenty-four-hour specimens. Two assays were also done on forty-eight-hour specimens for masculinizing hormone by the chloroform extraction method, 2 birds being used for each test, which showed 12 and 4, and 7 and 2 mm. comb growth, respectively. The average normal for men with this test is 10 mm. The Friedman test was negative.

A diagnosis of suspected adrenal tumor was made.

The right adrenal was explored. No evidence of cortical tumor or definite hypertrophy was found. A week later, both ovaries were removed. The right was found at operation to be about 6 cm. in diameter, covered by a firm capsule, containing 6 small hemorrhagic cysts. Section showed it to be made up of a rather yellow homogeneous mass, which appeared to contain connective tissue not resembling ovarian tissue. The left ovary was 4 cm. in diameter and was cystic. The cyst fluid was clear and yellowish.

There is still a woeful lack of knowledge concerning the nature of the unquestionably important relationship between the adrenal cortex and the gonads, and also the mechanism of the genital changes so characteristically seen with virilizing tumors of the adrenal cortex, in the well-known corticogenital syndrome. Recent studies upon the so-called androgenic zone of the adrenal suggest that perhaps a persistence of this zone, which in the human being disappears within the first year of life, may be concerned with the development of the corticogenital syndrome, and Broster and Vines,²⁹ as well as other authors, have made efforts to identify the cells of the androgenic zone by a special fuchsinophile stain. In the present state of our knowledge, it is scarcely worth while elaborating on this point, or in discussing various other hypotheses as to the mechanism involved in the corticogenital syndrome.³⁰

As regards arrhenoblastoma, we are even more in the dark as to the underlying cause for the neoplastic awakening of potentially testicular elements in the ovarian medulla. In passing, however, it may be mentioned that in at least one reported case, that of Gnassi, several separate arrhenoblastomas were present in one ovary, suggesting that some extraovarian factor might have been responsible for this multicentric neoplasm. One would naturally think of the adrenal as most likely to be the source of this extraovarian stimulus, but thus far there has been no histologic evidence to substantiate such a view.

From a diagnostic standpoint, it is clear that even with a definite history of defeminization and masculinization, associated also with the finding of an ovarian neoplasm, there is no way as yet to differentiate with any precision between adrenal ovarian tumors and arrhenoblastomas. Hormone studies may perhaps make this possible in the future. Thus far there is little or no information of significance as to the urinary hormone characteristics of either tumor type. There is little reason, moreover, to think that adrenal adenomas of the ovary would exhibit the high estrogen urinary concentration which Frank looks upon as characteristic of malignant cortical tumors of the adrenal.

SUMMARY

This paper is based primarily on the study of 11 cases of arrhenoblastoma, including the 6 new cases here reported. This group raises the total number of cases in the literature from 45 to 51, although instances of this interesting tumor type are being recorded with increasing frequency. The characteristic biologic effect of this neoplasm is to produce defeminization and masculinization phenomena. Chief among the former are amenorrhea, retrogression of the mammary glands, and loss of the feminine contour. Of the masculinization effects, the most striking are hirsutism, deepening of the voice, and hypertrophy of the clitoris. Removal of the tumor is followed by a return to normality, though this may not always be complete. In a small minority

mature functioning lutein cell, notoriously a very evanescent structure, could be the source of tumor growth. There is no doubt that certain granulosa cell cancers can exhibit a lutein-like transformation of the constituent cells, and this may be so complete that the tumor might be converted into a lutein-cell tumor. I have seen such a histologic transformation in parts of tumors which primarily are clearly of the granulosa-cell variety, so that there would seem to be no doubt of its possibility.

On the other hand, in most of the tumors which have been reported as luteomas, such an explanation can be ruled out, and I agree with Schiller⁹ that with a very few possible exceptions, these tumors are of adrenal rather than lutein character. Schiller accepts only 3 cases from the previous literature (Schultze-Bingel, Sellheim, Cosacesco-Drăganescu-Georgescu-Dinischiotu) as probably luteomas. I have been impressed with the fact that in most of the ovarian adrenal tumors, such as the three I have described, and also in the case of adrenal ovarian "rest" reported in 1936 by Saphir and Parker,²⁸ the growths have had the structure of normal adrenal tissue, and that they have not been of the type of the so-called hypernephroma of the ovary. A number of the latter have been recorded, both primary and secondary, and commonly highly malignant. As with the so-called hypernephroma of the kidney, however, sex character alterations are usually absent. In some cases, the explanation of this lies in errors of pathologic diagnosis, for in both the ovary and kidney many tumors formerly diagnosed as hypernephroma are now looked upon as adenocarcinomas. There is no doubt that a certain type of ovarian adenocarcinoma, by the pale staining, large size and frequently alveolar arrangement of its cells, may closely simulate the appearance of adrenal tissue. Careful study of other parts of the tumor will, however, usually show the more or less typical gland architecture characteristic of adenocarcinoma.

Whether the genuinely adrenal tumors of the ovary are to be looked upon as adrenal rests or as adrenal adenomas, in the sense in which adenoma is now employed to designate localized collections of functionally over-active cells of various endocrine glands, is difficult to say. Aberrant adrenal tissue is not infrequently observed, such rests being especially frequent along the course of the ovarian or spermatic vessels. In the ovary itself they are rare. They are not so infrequent, however, in the broad ligament, and I have encountered two cases in which small islands of what is apparently typical adrenal tissue occur near the ovarian hilum (Fig. 17). In neither of these patients, however, was there the slightest suggestion of masculinization changes. The mere presence of normal adrenal tissue in the ovary therefore would probably not in itself seem sufficient to explain such changes as were observed in the three cases I have mentioned, and, since the islands were of considerable size and evidently neoplastic, they are probably best interpreted as adrenal adenomas of the ovary. Neither in the histologic picture nor in the clinical course is there any suggestion of malignancy.

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DISCUSSION

DR. JAMES RAGLAN MILLER, HARTFORD, CONN.—Since 1916 at the Hartford Hospital we have observed 10 granulosa-cell tumors, 2 Brenner tumors and 2 arrhenoblastomas. We have seen no adrenal ovarian tumors. Neither of the arrhenoblastomas have shown any signs of masculinization; on the contrary, one of the cases showed bleeding in the menopause. Consequently I believe Dr. Novak is right in taking the attitude that the term "arrhenoblastoma" should not be confined merely to those cases which show signs of masculinization.

Since both of our cases showed no signs of masculinization, I feel inclined to consider Halban's theory. He believed that the hormones of the adrenal cortex and of the arrhenoblastoma with which we are here concerned are not specific male activators but may activate either gonad. He assumed also that when a female shows masculinization effects she does so because at birth she was a potential hermaphrodite and the effect is caused by the stimulation of male gonadal rests in her ovary. If there be no male tissue capable of functional response she may show precocious puberty or accentuated female characteristics in much the same manner as do the granulosa-cell cases. Such effects are reported in the presence of adrenal cortical tumors. Halban's theory is quite opposed to the conception of Grollman who postulates a distinct "androgenic" or "X" zone of adrenal subcortical cells to which he attributes the masculinizing hormone.

The role of the interstitial cell is not yet fully established, for it is certain that masculinizing effects are less often observed where the interstitial cells are best developed. These cells are best seen in fetal life and in the undescended testis and are not conspicuous at puberty when one would expect them to be at their highest state of development if they control secondary sex characteristics.

of cases, even though the tumor is clearly an arrhenoblastoma from a histologic standpoint, abnormal sex changes may be almost or entirely absent.

The proper basis for the microscopic diagnosis of these tumors is a knowledge of the early embryology of the gonads, and only in this way can one appreciate the very different histologic appearance encountered in different tumors and often in different parts of the same tumor. All gradations are seen between a structure closely simulating that of normal testis (testicular adenoma), to pictures showing only incomplete efforts at tubular formation, to those of sarcoma-like appearance. The fact that all these variations may be seen in different tumors, producing the same biologic effect, and, for that matter, in different parts of the same tumor, is strong evidence not only of their kinship, but also of the probable correctness of Meyer's original hypothesis that the origin of arrhenoblastoma is from certain male-directed cells persisting in the medulla of the ovary, particularly in the region of the rete ovarii.

The clinical and pathologic characteristics of the tumor have been described, stress being laid upon the fact that regression of the symptoms is of rather crucial importance in the substantiation of the diagnosis. While the development of masculinization phenomena in a previously normal woman, coupled with the presence of an ovarian tumor, justifies a strong suspicion of arrhenoblastoma, such a diagnosis cannot be considered absolute, as has been discussed in the paper. It is not possible, for example, to eliminate the possibility of the rare ovarian tumor composed of adrenal tissue, of which 3 cases are reported in this paper. The clinical syndrome of this tumor type and that of arrhenoblastoma may be almost identical, though there is not the slightest histologic resemblance. It seems quite probable that the adrenal may in some as yet unknown way be linked up with arrhenoblastoma, or at any rate that it may play a part in the production of the characteristic symptomatology of this tumor.

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Estimation of the relative value of the various methods of delivery and treatment of placenta previa must depend upon the extent to which they allow reasonable adherence to these surgical principles.

In the past few years, a striking reduction in maternal and fetal mortality from placenta previa has occurred in most obstetric clinics. This has been possible because:

1. Routine procedures have been put into effect from the time symptoms appear until delivery has been accomplished, thereby reducing the incidence of infection from all the usual sources.
2. The technique of blood transfusion has been improved until it is now a relatively simple, safe procedure.
3. In addition to blood transfusion, other effective methods for the treatment of surgical shock have been made readily available.
4. The incidence of undesirable results, from the trauma of vaginal delivery, has been reduced through perfection of the technique of operative obstetric procedures.
5. Improvements in the technique of cesarean section have increased the safety of suprapubic delivery and have allowed its more extensive use.

Many obstetricians have adopted cesarean section as an almost routine procedure for the treatment of central placenta previa and as the method of choice for the treatment of selected cases of partial and marginal varieties.

The advantages claimed for delivery by cesarean section are that:

1. Delivery without allowing the lower uterine segment to dilate tends to retain the limited hemostatic power which it possesses.
2. Delivery is quickly accomplished, reducing blood loss before and during delivery. Hemorrhage can be more promptly and positively controlled.
3. Cesarean section, particularly with incision in the lower uterine segment, allows inspection of the placental site. Active bleeding from sinuses can be controlled by suturing and packing under direct vision.
4. Undesirable or dangerous complications resulting from trauma of vaginal delivery are avoided.
5. Maternal morbidity and infection, the result of manipulation and contamination by vaginal procedures, is eliminated.
6. Fetal mortality, especially in central placenta previa, is strikingly reduced.

As difference of opinion still exists as to the most suitable method of delivery for the various types of placenta previa, it was decided to conduct a combined study of the end results of treatment of 400 such cases occurring at the Woman's Hospital in the past twenty-one years and at the Sloane Hospital for Women in the past seventeen years.

Table I shows the number and incidence of cases of placenta previa occurring at these two institutions within the periods of time stated above.

TABLE I. INCIDENCE OF PLACENTA PREVIA

	NUMBER OF DELIVERIES	PLACENTA PREVIAS	INCIDENCE
Woman's Hospital	25,388	185	1 in 137
Sloane Hospital	33,932	215	1 in 158
Total	59,321	400	1 in 148

END RESULTS IN 400 CASES OF PLACENTA PREVIA*

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IMPLANTATION of the placenta in the lower uterine segment still constitutes one of the most serious complications to be met in the practice of obstetrics.

Facts regarding the development of our scientific knowledge of placenta previa, the theories as to its causation, the symptomatology, and the accepted methods of treatment are too familiar to require discussion.

Accumulated experience has established facts which, in the treatment of placenta previa, cannot safely be disregarded. These facts may be briefly summarized as follows:

1. Implantation of the placenta in the lower uterine segment tends to interfere with proper engagement of the presenting part and is not infrequently associated with an abnormal presentation of the fetus.

2. Post-partum control of bleeding from the placental site depends upon firm contraction of the superimposed uterine musculature.

3. The lower uterine or passive segment of the uterus has very little hemostatic contracting power. Conditions associated with placenta previa further reduce physiologic hemostasis and predispose to excessive bleeding from the placental site.

4. Abnormal adherence of a placenta attached to the lower uterine segment occurs occasionally and may be a serious complication at time of delivery.

5. Atony of uterine musculature, which may follow excessive blood loss and surgical shock, tends to increase bleeding from the uterus and especially from the placental site.

6. Conditions associated with implantation of the placenta in the lower uterine segment predispose to cervical injury, rupture of the uterus, and infection during the course of labor and delivery.

Although this condition has been known since the time of Hippocrates, perhaps the most significant advance in the treatment of placenta previa has occurred in the past quarter of a century. Within this period of time, there has developed a better appreciation of the importance of consistently treating placenta previa in accordance with sound surgical principles. These principles include: (1) Prevention of infection. (2) Prevention of unnecessary hemorrhage and adequate replacement of blood loss. (3) Prevention and treatment of surgical shock by blood transfusion and other methods. (4) Avoidance of unnecessary trauma.

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

Classification was based upon physical findings at the time the condition was diagnosed. In many cases findings by vaginal examination were checked by recorded findings when cesarean section was done.

According to the classification outlined above, the 400 cases studied were classified as shown in Fig. 1.

It is interesting to note that approximately one-half (52.8 per cent) of the cases were classified as marginal, one-fifth (19.5 per cent) as partial, and one-fourth (27.7 per cent) as central placenta previa.

Fig. 2 shows the incidence of all cases studied in relation to age. At both institutions the maximum incidence occurred in the twenty-five- to thirty-year age groups.

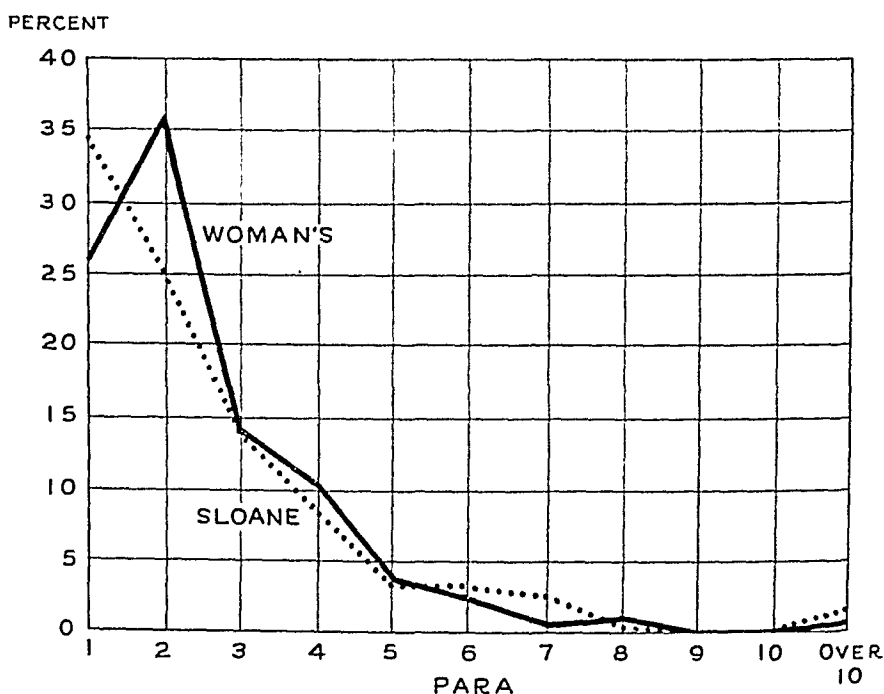


Fig. 3.—Parity in 400 cases of placenta previa.

Table II shows the age groups with maximum incidence in relation to type of placenta previa.

Fig. 3 shows the incidence of cases studied in relation to parity.

In the Woman's Hospital series the maximum percentage of cases of all types were at or near term with their second pregnancy, and in the Sloane series the greatest incidence occurred during the first pregnancy.

TABLE II. AGE GROUPS WITH MAXIMUM INCIDENCE IN 400 CASES OF PLACENTA PREVIA

TYPE OF PREVIA	AGE GROUP	
	WOMAN'S HOSPITAL	SLOANE HOSPITAL
Marginal	30-35	25-30
Partial	25-30	25-30
Central	35-40	25-30
Total	25-30	25-30

As a uniform classification of the various types of placenta previa has not been universally adopted by obstetrical authorities, it will be necessary to state that the classification which was used for this study was as follows:

1. *Marginal* where a part of the placenta was implanted in the lower uterine segment but the edge did not extend beyond the margin of the internal os.
2. *Partial* when part of the opening of the cervix was covered by placenta.
3. *Central* when the internal os of the cervix was completely covered by placenta.

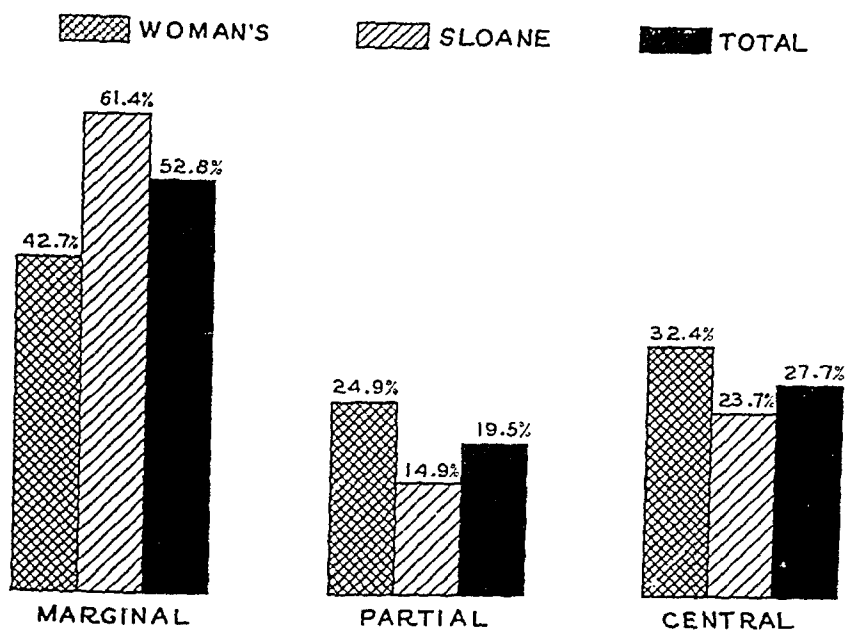


Fig. 1.—Classification by type in 400 cases of placenta previa.

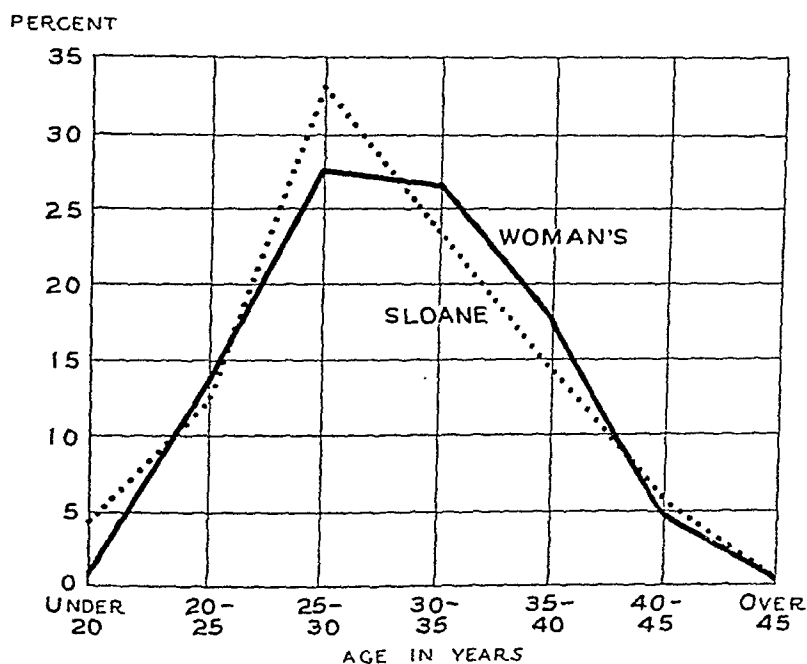


Fig. 2.—Age incidence in 400 cases of placenta previa.

Table IV shows the distribution of cases in relation to type of delivery employed. The number of deaths occurring after the various methods of delivery is also recorded.

Voorhees' bags were used to induce labor and to control hemorrhage in approximately one-half (52.5 per cent) of the cases delivered by vagina.

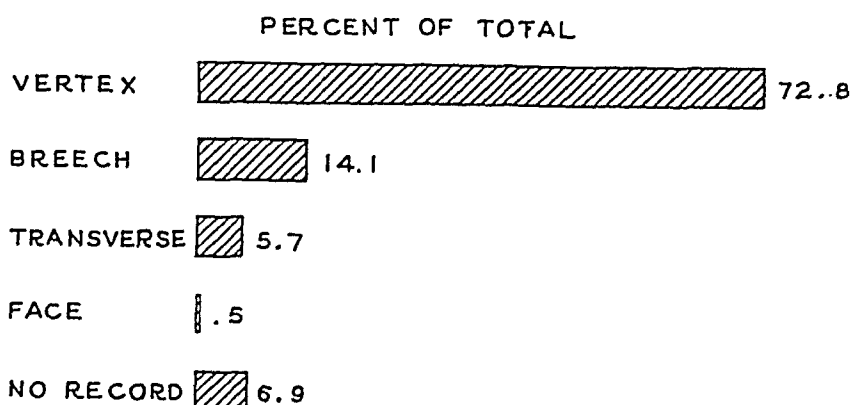


Fig. 5.—Presentation when symptoms appeared in 400 cases of placenta previa.

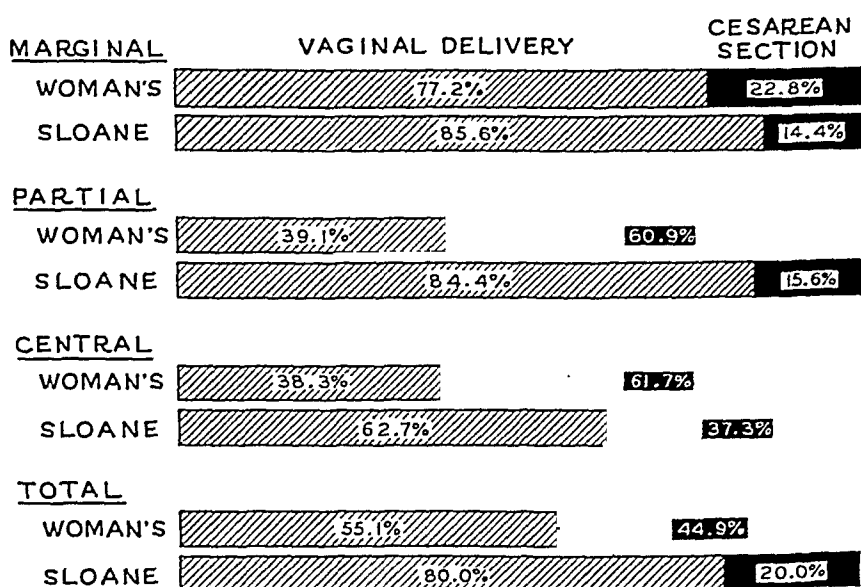


Fig. 6.—Incidence of vaginal delivery vs. cesarean section in 400 cases of placenta previa.

In Fig. 6 the incidence of vaginal deliveries vs. cesarean sections is shown.

It will be noted that in the Woman's Hospital series approximately 60 per cent of both partial and central placenta previa cases were delivered by cesarean section. At the Woman's Hospital 44.9 per cent of all cases were delivered by cesarean section, while at Sloane only one-fifth (20.0 per cent) was delivered by this method.


Table III shows the parity groups with maximum incidence in relation to type of placenta previa.


TABLE III. PARITY GROUPS WITH MAXIMUM INCIDENCE IN 400 CASES OF PLACENTA PREVIA

TYPE OF PREVIA	PARITY GROUP	
	WOMAN'S HOSPITAL	SLOANE HOSPITAL
Marginal	Para ii	Para i
Partial	Para ii	Para ii
Central	Para i	Para i
Total	Para ii	Para i

Of the patients treated 67.5 per cent were multiparous women. Multiparity has been considered an important predisposing factor in placenta previa. It is interesting to note that about one-third (32.4 per cent) of the cases treated occurred in women at or near term with their first pregnancies. The rather high incidence of placenta previa occurring in the first and second pregnancies may in part be due to

WEEKS NO. OF CASES


UNDER 24  13

24 - 28  16

28 - 32  51

32 - 36  77

36 - 40  233

OVER 40  10

CASES DELIVERED AFTER
28TH WEEK OF PREGNANCY

	NO.	%
WOMAN'S	171	92.4
SLOANE	200	93.0
TOTAL	371	92.7

Fig. 4.—Period of gestation at time of delivery in 400 cases of placenta previa.

the fact that, in admitting patients to the obstetric services at both hospitals, preference is given to patients having their first or second child and patients having previous difficult confinements.

Fig. 4 is a summary of the incidence of cases studied in relation to the periods of gestation at time of delivery.

The relative high incidence of abnormal presentation, as shown in Fig. 5, confirms the fact that implantation of the placenta in the lower uterine segment may interfere with engagement of the presenting part and complicate delivery by vagina.

dications for cesarean section or which would have seriously complicated delivery by vagina.

Table V is a summary of the incidence of maternal deaths in cases delivered by vagina as compared to those delivered by cesarean section.

TABLE V. MATERNAL MORTALITY RATE IN 400 CASES OF PLACENTA PREVIA

	VAGINAL DELIVERY			CESAREAN SECTION		
	NO. OF CASES	DEATHS	PER CENT	NO. OF CASES	DEATHS	PER CENT
<i>Woman's</i>						
Marginal	61	1	1.6	18	1	5.5
Partial	18	2	11.1	28	1	3.6
Central	23	3	13.0	37	4	10.8
Total	102	6	5.9	83	6	7.2
<i>Sloane</i>						
Marginal	113	2	1.8	19	0	0.0
Partial	27	2	7.4	5	0	0.0
Central	32	3	9.4	19	2	10.5
Total	172	7	4.1	43	2	4.6

Although cesarean section is gaining in popularity as a method of delivery for placenta previa, it would appear from the results of this series that delivery by vagina is a safer procedure. However, from a study of the facts regarding the treatment of the patients that died following cesarean section, it is obvious that the deaths which occurred were due not so much to the operation itself as to poor judgment in applying this method of delivery.

Eight of the 21 deaths in the series followed delivery by cesarean section. Of these 8 deaths, 4 were from hemorrhage and shock, 3 from sepsis, and 1 from acute yellow atrophy of the liver. By present-day methods of handling these cases it seems possible that any or all of these deaths might have been prevented.

The results of delivery by cesarean section, in more recent years, have been much more satisfactory as shown in Table VI. This table

TABLE VI. TREND OF MATERNAL MORTALITY IN 185 CASES OF PLACENTA PREVIA AT WOMAN'S HOSPITAL

	NUMBER OF CASES	DEATHS	PER CENT
Vaginal delivery			
1917-1923	34	4	11.8
1924-1930	47	2	4.2
1931-1937	21	0	0.0
Total	102	6	5.9
Cesarean section			
1917-1923	6	2	33.3
1924-1930	19	2	10.5
1931-1937	58	2	3.4
Total	83	6	7.2
Total			
1917-1923	40	6	15.0
1924-1930	66	4	6.1
1931-1937	79	2	2.5
Total	185	12	6.5

TABLE IV. MATERNAL MORTALITY BY METHOD OF DELIVERY IN 400 CASES OF PLACENTA PREVIA

METHOD OF DELIVERY	NUMBER OF DELIVERIES	MATERNAL DEATHS
Vaginal delivery—Total	274	13
Normal	82	2
Breech	40	3
Forceps—Low	27	0
Mid	17	0
High	5	0
Version and breech extraction	102	8
Vaginal hysterotomy	1	0
Cesarean section—Total	126	8
Classical	65	4
Low flap	57	3
Peritoneal exclusion	1	1
Porro	3	0
Total	400	21

TABLE IVA. MARGINAL AND PARTIAL PLACENTA PREVIA—INDICATIONS, IN ADDITION TO PLACENTA PREVIA, FOR DELIVERY OF 70 CASES BY CESAREAN SECTION

COMPLICATIONS	WOMAN'S HOSPITAL		SLOANE HOSPITAL	
	MARGINAL	PARTIAL	MARGINAL	PARTIAL
1. Feto-maternal disproportion:				
Contracted pelvis	5	4		
Large babies (weight 8 pounds 11 ounces to 9 pounds 4 ounces)	1	2	6	1
2. Previous pelvic operations:				
High amputation cervix		1		
Pregnancy after Watkin's interposition		1		
Retroversion operation for sterility and repeated abortion	1			
Previous cesarean section	1		1	
3. Abnormal presentation	1	2	2	1
4. Elderly primiparas (37-40 years)	2	5	2	
5. Previous complicated deliveries	1	1	1	
6. Cardiac disease	2	3		
7. Toxemia of pregnancy	2		1	
8. Fibroids			2	
9. Sterilization			1	
10. Safety of mother and baby:				2
Moderate to profuse bleeding before or during labor		7	1	
Cervix unsuitable for bag	2	1	2	
Fetal distress		1		1
Total number of cesarean sections	18	28	19	5

In Table IVA it will be noted that at the Woman's Hospital only 11 (24 per cent) of the 46 cases of marginal and partial placenta previa without other complications were delivered by cesarean section. At Sloane only 6 (25 per cent) of the 24 cases of marginal and partial placenta previa delivered by cesarean section were free of other complications.

In other words in both series approximately three-fourths of such patients had complications which in themselves were acceptable in-

TABLE VIIA. SUMMARY OF MATERNAL DEATHS

CASE	TYPE OF PREVIA	AGE	PARA	PERIOD OF GESTATION (WEEKS)	METHOD OF DELIVERY	COMPLICATIONS AND CAUSE OF DEATH	TIME OF DEATH	CRITICISMS OF TREATMENT
<i>Woman's Hospital Series</i>								
1	Central	39	vi	40	Bag, version and breech extraction	Hemorrhage and shock	Died on table	No preparation for transfusion until patient was in shock from hemorrhage
2	Central	No record	vi	36	Bag, version and breech extraction	Hemorrhage and shock	3 hr. after delivery	In serious condition before delivery. No preparation made for transfusion
3	Marginal	41	ii	40	Version and breech extraction	Hemorrhage and shock	1 day	No preparation for transfusion. Profuse hemorrhage
4	Central	33	v	42	Low flap cesarean section	Transverse presentation. Hemorrhage and shock. Baby 11 pounds 10 ounces	20 min. after delivery	Transfused at end of operation. Control of bleeding by packing and delay of operation for treatment of shock might have been a life-saving measure
5	Central	35	i	38	Low flap cesarean section	P.P. Extraperitoneal hemorrhage, shock, acute yellow atrophy liver. Autopsy	9 hours after delivery	Transfusion 9 hours after delivery. Earlier transfusion might have controlled predisposition to bleeding with acute yellow atrophy
6	Marginal	27	i	36	Low flap cesarean section	Shock and circulatory collapse. Myocardial disease with decompensation in A.P. period	Died day operation	Went into shock during operation. Preparation for transfusion started after patient was in serious condition
7	Partial	26	No record	35	Bag, version and breech extraction	Pulmonary embolism	Died on table	Death accidental. Probably not preventable
8	Central	37	v	32	Packing, bag and breech delivery	Acute nephritis. Iodoform poisoning. Coronary embolism. Autopsy	8 days	Packing 6 post-partum days unnecessary, probably fatal to sensitive patient

shows the striking improvement in results of treatment in three successive seven-year periods at the Woman's Hospital. It is believed that better results have been due to more extensive use of cesarean section and to prevention and better treatment of hemorrhage and shock.

Table VII is a summary of the incidence and causes of maternal deaths after delivery by vagina and cesarean section.

TABLE VII. CAUSES OF MATERNAL DEATHS IN 400 CASES OF PLACENTA PREVIA

	WOMAN'S	SLOANE	TOTAL
<i>Deaths After Vaginal Delivery</i>			
No. of deliveries	102	172	274
Cause of death			
Hemorrhage and shock	3	5	8
Embolism	3*	0	3
Septicemia	0	2	2
Total—Number	6	7	13
Per cent	5.9	4.1	4.7
<i>Deaths After Cesarean Section</i>			
No. of deliveries	83	43	126
Cause of death			
Hemorrhage and shock	3†	1	4
Acute yellow atrophy	1	0	1
Acute general peritonitis	1	0	1
Septicemia and paralytic ileus	1	1	2
Total—Number	6	2	8
Per cent	7.2	4.6	6.3

*Other complications: Acute nephritis 1; phlebitis 1.

†Other complications: Acute yellow atrophy 1; Myocarditis, chronic 1.

Table VIIA is a summary of facts regarding patients that died.

Study of the records of the 21 patients who died shows that 12 died of hemorrhage and shock. Ten of these patients had no other complications. Of the 12 patients, 8 were delivered by vagina and 4 by cesarean section. One patient, delivered by cesarean, had chronic myocarditis, and had been hospitalized during pregnancy for cardiac decompensation. However, the immediate cause of death in this case was hemorrhage and shock. Another patient delivered by cesarean section died following post-partum extraperitoneal hemorrhage, estimated at 300 c.c. at autopsy. Although she had acute yellow atrophy she was apparently progressing satisfactorily until the post-partum hemorrhage occurred. In other words more than one-half of the deaths in the series were the result of hemorrhage and shock.

One of these 12 patients was transfused before delivery and one immediately after cesarean section. In none of the remaining 10 cases was preparation started for transfusion until the patient had bled excessively during or after delivery and had developed some degree of surgical shock.

With present-day handling it seems reasonable to consider all of the 12 deaths, as a result of hemorrhage and shock, as possibly preventable.

Three of the 21 deaths were from emboli in patients delivered by vagina. One occurred at the end of delivery and was probably unavoidable. A second patient died from embolism on the eighth post-partum day after having developed acute nephritis from iodoform packing left in the uterus for six days. The third death was due to embolism on the twenty-fourth post-partum day in a patient who had an infected perineal wound and phlebitis. It should probably be considered a death from sepsis.

TABLE VIIA.—CONT'D

CASE	TYPE OF PREVIA	AGE	PARA	PERIOD OF GESTATION (WEEKS)	METHOD OF DELIVERY	COMPLICATIONS AND CAUSE OF DEATH	TIME OF DEATH	CRITICISMS OF TREATMENT
5	Central	22	ii	40	Bag, version and breech extraction	Contracted pelvis. Large baby 8 pounds 7 ounces. Hemorrhage and shock. Ruptured uterus. Autopsy	Day of delivery	Poor condition on admission. Three transfusions total 1810 c.c. Delivery before full cervical dilatation. Cervix and uterus not examined for injury. Delivery by cesarean justifiable and safer
6	Marginal	30	iv	28-30	Breech extraction	Long, rigid cervix. Prolonged labor (118 hr.). Hemorrhage and shock.	On table	Three transfusions, total 2,100 c.c. Breech extraction without full dilatation of cervix. Trachelorrhaphy. Bag might have helped cervical dilatation. Cesarean section might have been justifiable
7	Partial	20	i	36	Dührssen's incisions Breech extraction	Profuse hemorrhage at operation. Sepsis and exhaustion	11 days	Mother febrile (99°-100.2°) during 6 days' observation. Intrauterine death of fetus (3 pounds 2 ounces). Bleeding had ceased. To await spontaneous delivery might have been safer
8	Central	33	ii	40	Classical cesarean section	Sepsis (paralytic ileus). Immediate cause of death incompatible blood?	6 days	Profuse bleeding before delivery. No transfusion until sixth p.p. day. Earlier and repeated transfusions might have prevented fatal outcome.
9	Marginal	26	iv	29	Bag, spontaneous delivery	Temperature at 104° end of delivery. Septicemia (Hemolytic streptococcus)	14 days	Infected on admission. Six transfusions. Death probably inevitable

TABLE VIIA.—CONT'D

9	Partial	33	i	38	Breech delivery	Phlebitis. Pulmonary embolism. Infected wound	24 days	In spite of marked secondary anemia, no transfusion until fifteenth p.p. day
10	Central	32	v	28	Classical cesarean section	Acute yellow atrophy. Suppression urine. (26 ounces in 8 p.p. days)	8 days	With symptoms of acute yellow atrophy delivery was delayed too long in order to get living child
11	Partial	32	ii	36	Classical cesarean section	Acute general peritonitis	6 days	Potentially infected on admission. Classical cesarean section, unwise method of delivery
12	Central	30	iii	40	Cesarean section portotomeal exclusion	Uremia. Septicemia. Paralytic ileus	8 days	Excessive bleeding before and at delivery, estimated over 2,000 c.c. One transfusion 550 c.c.

<i>Sloane Hospital Series</i>								
1	Marginal	32	i	40	Bag, packing, version and breech extraction	Lacerated cervix. Hemorrhage and shock	40 hours after delivery	Delivered when cervix was four fingers dilated. Transfusion not given until day after delivery
2	Central	22	i	40	Bag and packing. Classical cesarean section	Hemorrhage and shock	2 hours after delivery	Elective cesarean section justifiable with male pelvis and central previa. Transfusion before operation might have prevented fatal hemorrhage and shock
3	Central	22	i	28	Spontaneous delivery	Marked secondary anemia. Hemorrhage and shock.	7 hours after delivery	Serious condition during labor. Not given transfusion until one hour after delivery
4	Central	29	iv	36	Bag, packing, version and breech extraction	Hemorrhage and shock	Day of delivery	Version through cervix dilated 6 cm. (profuse hemorrhage). One transfusion, 400 c.c., inadequate replacement of blood loss

TABLE VII.B. FETAL MORTALITY. SURVIVAL OF VIABLE BABIES AFTER DELIVERY BY VAGINA *vs.* CESAREAN SECTION

	WOMAN'S			SLOANE		
	MARGINAL	PARTIAL	CENTRAL	MARGINAL	PARTIAL	CENTRAL
<i>Delivery by Vagina</i>						
No. of deliveries	61	18	23	113	27	32
No. of babies	62	19	23	114	27	32
	(1 set of twins)	(1 set of twins)				
Nonviable babies	7	2	5	7	0	6
Viable babies	55	17	18	107	27	26
Stillbirths	3	3	6	28	13	17
Neonatal deaths	8	3	6	4	2	5
Survived	44	11	6	75	12	4
Survived, viable babies in percentages	80.0	64.7	33.3	70.0	44.4	15.3
Survival all types by vaginal route, 67.7					56.8	
<i>Delivery by Cesarean Section</i>						
No. of deliveries	18	28	37	19	5	19
No. of babies	18	29	37	19	5	20
		(1 set of twins)				
Nonviable babies	0	1	0	0	0	0
Viable babies	18	28	37	19	5	20
Stillbirths	0	2	1	0	0	3
Neonatal deaths	1	1	7	0	0	0
Survived	17	25	29	19	5	17
Survived, viable babies in percentages	94.4	89.2	78.3	100.0	100.0	85.0
Survived all types after cesarean section, 85.5					93.11	

TABLE VIII.—SURVIVAL OF VIABLE BABIES AFTER VAGINAL DELIVERY *vs.* CESAREAN SECTION IN 400 CASES OF PLACENTA PREVIA

TYPES OF PLACENTA PREVIA	WOMAN'S HOSPITAL		SLOANE HOSPITAL	
	VAGINAL DELIVERY	CESAREAN SECTION	VAGINAL DELIVERY	CESAREAN SECTION
Marginal	80.0	94.4	70.0	100.0
Partial	64.7	89.2	44.4	100.0
Central	33.3	78.3	15.3	85.0
Total	67.7	85.5	56.8	93.2

disaster. Experience proves that delivery under such conditions to save the child is unjustifiable.

Patients with organic disease complicated by pregnancy and placenta previa present problems to test the skill and judgment of the most competent obstetrician. Such patients must be individually considered in order to decide upon the most suitable time and method of delivery.

Potentially or actually infected patients are serious risks regardless of the method of delivery. If they are to be delivered by the abdominal route, Porro cesarean section rather than the classical or low flap types of operation should be employed. Although we have had no experience with extraperitoneal cesarean section in this type of

One of the 21 deaths was the result of acute yellow atrophy of the liver. In view of the toxic symptoms delivery was postponed too long in an effort to get a viable baby.

Five of the 21 deaths were definitely the result of sepsis. Of the 2 septic deaths after vaginal delivery, one had symptoms of infection on admission and death was probably inevitable. The other occurred after Dührssen's incision and breech extraction in a case which failed to respond satisfactorily to attempts at induction. With a febrile (99° to 100.2°) mother during six days of observation before induction was attempted, intrapartum death of a 3 pound 2 ounce fetus and cessation of hemorrhage, it might have been safer to wait for spontaneous cervical dilatation. Two septic deaths followed classical cesarean section. One of these patients had an adherent placenta and profuse bleeding at delivery but no transfusion until the sixth post-partum day. The other classical cesarean section was unwisely chosen as the method of delivery in a patient with a definite potential infection. Vaginal delivery or Porro cesarean section would have been safer.

It is evident from the records that the patients who developed sepsis could have had much better post-partum care. In 4 of the 5 cases replacement of blood loss was inadequate or was delayed until sepsis developed. It seems obvious that adequate replacement of blood loss may be as important in preventing dangerous post-partum complications as in the prevention of surgical shock. A depleted post-partum patient should be transfused, and repeatedly transfused if necessary, for the prevention of complications as well as for their treatment.

Table VIIB shows the outcome of babies delivered by vagina vs. cesarean section in the three types of placenta previa. In the Woman's Hospital series with its higher incidence of cesarean section, a total of 76.3 per cent of viable babies survived as compared to 64.7 per cent in the Sloane series.

Table VIII is a summary of the survival of viable babies after vaginal delivery vs. cesarean section.

From a study of end results it is difficult to formulate an accurate opinion of the success of the various methods of treatment for any obstetric condition. This is true because results are usually based upon survival of patients treated.

It is obvious from this series of cases that most of the patients that died as well as many that survived were carried through labor, delivery, and the post-partum period with too narrow a margin of safety.

The outstanding fault of treatment was the failure to provide adequate replacement of blood loss. The condition of many patients at time of delivery was such that even moderate additional blood loss was sure to throw them into dangerous or fatal shock. Others were actually in shock when delivered by vagina or cesarean section.

Patients with placenta previa are usually admitted to a hospital with a history of painless bleeding either at or before the onset of labor. Excessive bleeding can almost invariably be controlled by packing and bags for a sufficient period of time to allow blood transfusion before delivery and preparation for subsequent transfusions. Delivery of a patient with marked anemia or while in shock invites

placenta covers 50 per cent or less of the cervical canal; and Partial II, 50 per cent or more. The marginal and central types do not need to be subdivided.

Ude and Urner have recently recommended cystograms in the diagnosis of placenta previa. We have used this method at the Methodist Episcopal and Long Island College Hospitals in well over 100 cases. This method is important and gives some valuable information, but it is not always absolutely accurate. If the x-ray shows a sinking down of the head in the lower segment, one can definitely say there is no placenta previa. On the other hand, if there is a space of from 1.5 to 2.5 cm., it may or may not be placenta previa.

These patients should under proper precautions, have a pelvic examination through the vagina. In Brooklyn there is some agitation for not examining placenta previa cases. There are conditions, of course, where vaginal examinations should not be made, but examination is obligatory in the vast majority of cases. We teach and practice that "without a correct diagnosis there can be no intelligent treatment."

Minimizing trauma is most important, and of course, it is much more important to prevent infection than to treat it. Likewise, the prevention of shock is more important than its treatment, and if present it should be treated immediately. The longer shock is present the less likely the patient is to survive. Heat, morphine, and blood transfusion are essential. As an illustration, only last week we had a patient with a ruptured uterus in profound shock. In forty-five minutes she had been given 2,000 c.c. of blood and had had a hysterectomy. The next morning she sat up and ate her breakfast.

There is no question but that cesarean section is gradually coming into its own. There is also no question that one must have the conditions that call for section.

DR. NORRIS W. VAUX, PHILADELPHIA, PA.—Dr. Aldridge's review indicates clearly the very definite improvement in maternal and fetal mortality from this complication of pregnancy, in two outstanding maternity hospitals in the United States, in the last ten years.

I approve the use of vaginal examination in cases of placenta previa, provided no undue risk is entailed and proper preparation of the patient and attendants has been strictly enforced. It is imperative that all preparations and equipment necessary for combating secondary hemorrhage following vaginal examination, be at hand.

I have been for years an advocate of the more radical procedure of operative delivery. Yet I fully realize that all cases of placenta previa are not necessarily close to a well-equipped institution where this method of procedure can be safely carried out. I therefore wish to emphasize the importance of conservative treatment in all such instances.

I am glad that your attention has been called to the added risk associated with vaginal, as compared with abdominal, delivery in cases of placenta previa. Cesarean section does, without a doubt lessen the risk of uterine infection as well as trauma of the lower uterine segment and of the cervix. The close relationship of the placental site in the lower uterine segment to the vagina increases the risk of any vaginal manipulation. Cesarean section also eliminates the danger of rupture of the uterus at the placental site.

It is interesting to note that in 33,012 patients delivered in the Jefferson Maternity and the Philadelphia Lying-In Hospitals, in approximately ten years, there were 166 patients with proved placenta previa (marginal, partial, or central), an incidence of one placenta previa case in every 198 deliveries, which is somewhat less than the incidence in either the Woman's Hospital or the Sloane Maternity. There were 11 maternal deaths in our series, a maternal mortality of 6.6 per cent. One of these cases was moribund on admission and died undelivered. In comparing the vaginal delivery deaths (4.9 per cent) in placenta previa with those delivered by the abdominal route, the percentage of cesarean section deaths (8.3 per cent) is somewhat higher. Maternal mortality rose very definitely in those individuals in whom there was a serious delay in replacement of blood loss when secondary hemor-

case, it is possible that it may eventually offer a conservative means of delivery for at least the potentially infected cases.

To summarize it may be stated that:

1. Placenta previa constitutes one of the most serious complications to be met in obstetric practice.

2. Patients should be treated according to sound surgical principles for the prevention of infection, unnecessary hemorrhage, surgical shock, and trauma.

3. Patients should be prepared as carefully for vaginal delivery or cesarean section as for any major surgical operation.

4. Blood transfusion provides the most effective means for the prevention and treatment of surgical shock. Other means of treating shock should be readily available in every obstetric hospital to protect patients while preparations for blood transfusion are being made.

5. Delivery by vagina or cesarean section of a patient in shock or seriously depleted by hemorrhage should not be undertaken until adequate replacement of blood loss has been accomplished.

6. Complications resulting in dangerous hemorrhage may be unexpectedly encountered during delivery. Provision for blood transfusion during operation may prevent disaster.

7. Cesarean section offers a valuable means of delivery of patients with central placenta previa and selected cases of partial and marginal placenta previa.

8. Placenta previa frequently occurs in patients who have physical conditions which either constitute acceptable indications for cesarean section or which may seriously complicate delivery by vagina.

9. Fetal mortality is strikingly reduced in patients delivered by cesarean section.

10. Blood transfusion to combat anemia and to improve the general physical condition of patients following delivery may reduce the incidence and danger of post-partum complications.

11. Conditions associated with placenta previa demand hospital treatment for safety.

DISCUSSION

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—During the past five years there were 8,410 deliveries at the Methodist Episcopal Hospital in Brooklyn, with 38 cases of placenta previa, giving an incidence of 1 in 221.

Our methods of management are similar to those of the last seven years of Dr. Aldridge's, namely, simple rupture of the membranes, the use of the Voorhees' bag or cesarean section. In these 38 cases there were no maternal deaths. There were 15 fetal deaths, a mortality of 31.5 per cent. We can justifiably correct this rate, because there were two macerated fetuses and five nonviable prematures, so that the corrected fetal mortality is 21 per cent.

Taking the cesarean sections separately there were 7 of the classical and 3 of the low flap type, a total of 10 cases with no maternal mortality and one fetal death. This baby was stillborn although the fetal heart was thought to have been heard shortly before operation.

I agree with Dr. Aldridge that we need a more accurate classification and would suggest subdividing the partial group by adding the terms Partial I, where the

I will not quarrel over the relative merits of direct or indirect transfusion. The important thing is to transfuse the patient immediately and as often as necessary. About one-fourth of our cases are transfused. Cesarean section is done in about one-fourth to one-third of our cases. Willett forceps and the Braxton Hicks version are used. Usually the bag is ruled out except where the life of the fetus is already extinct or of no particular value. The lower segment cesarean section is used more frequently in our hospital than the upper segment or classical type. The advantages of the one in giving access to the placental site, and of the other in keeping away from the placental site are admitted. Both methods give good results. While our results have been questioned in some quarters, nevertheless we have had practically no maternal mortality, and we believe that it can be reduced to practically nil, that the fetal mortality should not exceed 20 per cent uncorrected, and that the corrected mortality should be somewhere around 6 per cent.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—In determining the type of treatment, one should perhaps not attach so much importance to the degrees of placenta previa as to the condition of the cervix. Partial placenta previa with a rigid cervix may be a more serious condition than a complete placenta previa with a soft and retracted cervix. Therefore, I believe that a careful vaginal examination is called for in all cases and that the determination of treatment should depend upon the condition of the cervix more than upon the actual degree of placenta previa.

rhage occurred, and this possibly was the factor in the resultant fatal surgical shock and collapse. It would seem to me, therefore, that prompt replacement of blood to combat the surgical shock, regardless of vaginal or abdominal delivery, should not be long postponed after the initial hemorrhage.

I cannot agree that the method of choice in delivering placenta previa by the abdominal route is the low flap cesarean section. A more pronounced blood loss is likely to occur following this type of incision while a fundal or classical incision, which is far removed from the placental site, may give better results relative to the separation of placenta after delivery and the primary and immediate spontaneous involution of the uterus.

It is advisable to accept all painless bleeding in the last trimester of pregnancy as that of placenta previa until it has been proved otherwise, and as such the patient should be immediately hospitalized, for the sake of safety. Upon admission to a well-equipped institution, replacement of blood loss should be the first treatment instituted, and that without delay. The condition in which the patient is found at the time of admission and the type of placenta previa determined by examination, should be the indications for either temporary delay or prompt surgical intervention. No patient in surgical shock from blood loss associated with placenta previa should be considered an operative risk until the treatment instituted for surgical shock has become effective.

DR. F. C. GOLDSBOROUGH, BUFFALO, N. Y.—I want to emphasize the importance of correct diagnosis because of an experience I had recently in seeing a patient with a ruptured uterus in her second pregnancy. She had had, she said, a placenta previa in her first delivery. On account of a slight blood-tinged discharge she had been rushed into the hospital, and with a diagnosis of placenta previa, delivery was made by cesarean section. The proper diagnosis was the slight show of the onset of labor.

A second case was sent in with a diagnosis of placenta previa. As there was no hemorrhage on admission she was kept under observation. There was no further hemorrhage, the patient went to term and was delivered normally. The diagnosis in this case was decidua polyposa. In some hospitals she would have had an immediate cesarean, without a correct diagnosis.

DR. FRED L. ADAIR, CHICAGO, ILL.—When one attempts to classify according to the relation of the placenta to the cervical canal or os, there is a great deal of variation, dependent upon the stage of labor and the time the symptoms develop. Naturally the exposure of the placenta varies with the amount of dilatation. We have tried to simplify the classification as much as possible and to recognize only two groups of placenta previa, on the basis of the conditions found at the time the first symptoms develop. We recognize the type where the os is covered and the type where the os is not covered at that time. This serves as a fundamental basis for deciding the type of treatment required. In our classification there are only the complete and the incomplete types.

A point worthy of emphasis, in the early diagnosis, is the warning hemorrhage. Many cases of placenta previa have a show of blood and if one pays attention to this slight bleeding which occurs in the last trimester, without any other symptoms, one can usually forestall more serious hemorrhage. With any bleeding the patient should be brought to the hospital, if possible, and carefully examined in order to rule out a placenta previa. About one-fourth to one-third of these cases with warning bleeding have a placenta previa, and they are treated promptly.

There is no stereotyped form of treatment. The condition and the parity of the mother and the status of the fetus must all be taken into consideration. A cesarean section is not indicated where the life of the fetus is not at stake. Where the fetus is nonviable or dead or already in a serious condition, cesarean section should not be undertaken, as the condition, so far as the mother is concerned, can be treated successfully without it in most cases.

myomas of the uterus have been included under the general head of endometriosis, which will explain the high incidence of involvement of the uterus.

AGE INCIDENCE

Endometriosis is a disease that occurs principally during the reproductive period, the greatest number of patients being in the fourth and fifth decades of life. The fact that it is seen early in the third decade, however, makes it of increasing importance. Our youngest patient was 21 years of age, the oldest 73 (Table I).

TABLE I. ENDOMETRIOSIS: 1923-1937, 884 PATIENTS

AGE DISTRIBUTION

AGE YEARS	NUMBER	PER CENT
20-29	61	6.9
30-39	272	30.8
40-49	443	50.1
50-59	99	11.2
60-69	8	0.9
70+	1	0.1
Total	884	100.0
Mean age	41.9 years	
Youngest patient	21 years	
Oldest patient	73 years	

Seven hundred and fifteen patients (80.9 per cent) were between 30 and 50 years of age; 61 (6.9 per cent) were between 20 and 30, and 108 (12.2 per cent) were beyond 50. In this last group the lesions were mostly adenomyomas of the uterus, and the surgical treatment for this older group obviously was complete hysterectomy.

LOCATION OF THE LESIONS

The distribution of the lesions followed the same general pattern as given by previous authors who included adenomyomas of the uterus under the heading of endometriosis. The uterus was the most common site of involvement, there being 640 lesions of this organ and the cervix. The ovary was next with 120 lesions. In the group of 108 cases of diffuse endometriosis, it was impossible to give a

TABLE II. ENDOMETRIOSIS: 1923-1937, 884 PATIENTS

ANATOMIC LOCATION OF LESIONS

LOCATION	NUMBER	PER CENT OF PATIENTS*
Uterus	618	69.9
Cervix	22	2.5
Ovary (probably not complete)	120	13.6
Rectovaginal septum	27	3.0
Ligaments of uterus	22	2.5
Sigmoid, rectosigmoid, or rectum	24	2.7
Pelvic peritoneum	44	5.0
Vaginal wall	17	1.9
Fallopian tube	27	3.0
Umbilicus	6	0.7
Ileum	2	0.2
Appendix	1	0.1
Bladder	2	0.2
Diffuse	108	12.2

*More than one organ affected. The total, therefore, does not add to 100 per cent.

ENDOMETRIOSIS*

A CLINICAL AND SURGICAL REVIEW

VIRGIL S. COUNSELLER, M.D., ROCHESTER, MINN.

(From the Division of Surgery, the Mayo Clinic)

JUST eighteen years ago Dr. Sampson⁹ presented before this Society his observations on 23 patients with what he designated as "perforating hemorrhagic cysts" of the ovary and stated that, from these hemorrhagic cysts, pelvic adenomas took their origin. He expressed the opinion that he could not be sure that the ovarian hematomas were the only cause of ectopic adenomas. One¹⁰ year later he stated to this Society that ectopic pelvic adenomas originated also from menstrual elements extruded from the uterus through the oviducts and from tubal epithelium which become implanted on the ovary and other pelvic structures. He suggested the term "endometriosis" to designate this pathologic entity. This term has been generally accepted by gynecologists and pathologists.

Many students of the subject have not accepted Sampson's theory regarding the etiology of this disease but, nevertheless, a great debt is due him for stimulating so much interest in it. Most of the papers on the subject have dealt with theories of development, pathologic studies, the distribution of the lesions and the subjective symptoms, and relatively few have dealt with the results of treatment. Read and Roques (1929), Wharton (1929), Keene and Kimbrough (1930), Smith (1929), Cattell (1936), and Pemberton (1937) reviewed their clinical findings and published their results of radical and conservative surgical treatment. Since endometriosis is primarily a surgical disease, the methods involved in its management can be evaluated better and a clearer conception of its clinical importance can be brought about by publication of the results of treatment.

Masson reviewed the cases of 576 patients with endometriosis who were treated at the Mayo Clinic between 1923 and 1934. To this series I wish to add 308 additional cases of patients treated subsequently up to and including 1937. I will then discuss the entire series in somewhat greater detail and evaluate the results of conservative treatment.†

The generally accepted idea of endometriosis is of an abnormal growth of endometrial tissue in an ectopic position. Graves stated that the use of the term "endometriosis" assumes the acceptance of Sampson's theories of etiology. Blair Bell mentioned the term "endometrioma," which indicates tumor formation. In the present series of cases adeno-

*Read at the Sixty-third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

†I am greatly indebted to my assistant, Dr. R. E. Bedard, and to Dr. J. Berkson, of the Statistical Department, for their careful study of our case records and the resulting data.

TABLE III. MENSTRUAL ABNORMALITIES: 308 PATIENTS

(RECENT SERIES, 1935-1937)

	NUMBER	PER CENT OF TOTAL CASES
Menstrual abnormality:		
Menstrual abnormality (any type)	247	80.2
No menstrual abnormality	32	10.4
No information	29	9.4
Pain:		
Pain with menses	144	46.8
Pain increasing	57	39.6*
Pain worse on exertion	27	18.7*
Pain worse on defecation	21	14.6*
Pain worse on urination	7	4.9*
No pain with menses	74	24.0
No information	90	29.2
Menstrual disturbance:		
Menorrhagia and/or metrorrhagia	202	65.6
No menorrhagia or metrorrhagia	48	15.6
No information	58	18.8

*Based on 144 patients with pain.

ASSOCIATED PELVIC DISEASE

Menstrual disturbances are extremely difficult to evaluate, if one attempts to be at all accurate in attributing them to endometriosis, since 54.5 per cent of the 308 patients in the recent series had leiomyomas of sufficient size to account for such irregularity (Table IV). Furthermore, 60 per cent of the patients had lesions

TABLE IV. ASSOCIATED PELVIC DISEASE: 308 PATIENTS

(RECENT SERIES 1935-1937)

	NUMBER	PER CENT OF CASES*
Leiomyoma	168	54.5
Chronic cystic oophoritis	161	52.3
Simple cyst	24	7.8
Corpus luteum cyst	19	6.2
Atrophic oophoritis	12	3.9
Cystadenoma	7	2.3
Carcinoma of ovary	3	1.0
Tubo-ovarian abscess	2	0.6
Carcinoma of uterus	1	0.3
Carcinoma of cervix	1	0.3

*A single patient may have had more than one pathologic condition. The total therefore adds to more than 100 per cent.

of the ovaries other than endometriosis which might also have been responsible for the menstrual disturbance. We are of the opinion that it is reasonable to state that endometriosis per se does not produce disturbances in menstruation, although endometrial adenomas within the uterus itself probably do in some instances. In this series of 308 patients, 65.6 per cent had menorrhagia, metrorrhagia, or both (Table III), which is approximately the same percentage as that stated for the number of associated pathologic lesions of the uterus and ovary (Table IV).

PREVIOUS SURGICAL PROCEDURES

Since endometriomas occur in laparotomy wounds following operations on the uterus, it occurred to us that trauma as a direct result of operation on the pelvic organs or as a result of manipulation of the organs at the time of operation might

specific location to the lesion. Other sites of involvement were the rectovaginal septum in 27 instances, the umbilicus in 6 and the bladder in 2. Twenty-four lesions involved the sigmoid, rectosigmoid or rectum, and 44 involved the pelvic peritoneum (Table II).

DYSMENORRHEA

The clinical symptoms of endometriosis are variable and are determined largely by the location of the masses and the number of regions involved. Dysmenorrhea of the acquired type, with some degree of progression, is very suggestive of the disease. We at the clinic are convinced that in girls in the second and third decades at least, endometriosis is in many cases responsible for pelvic pain, although the lesions are not firm enough to palpate either vaginally or rectally. I rather suspect that in many such cases the pain is due to endometrial growths within the myometrium, as depicted in Fig. 1. This patient, aged 22 years, had been treated for five years for extreme dysmenorrhea without effect and the family had requested

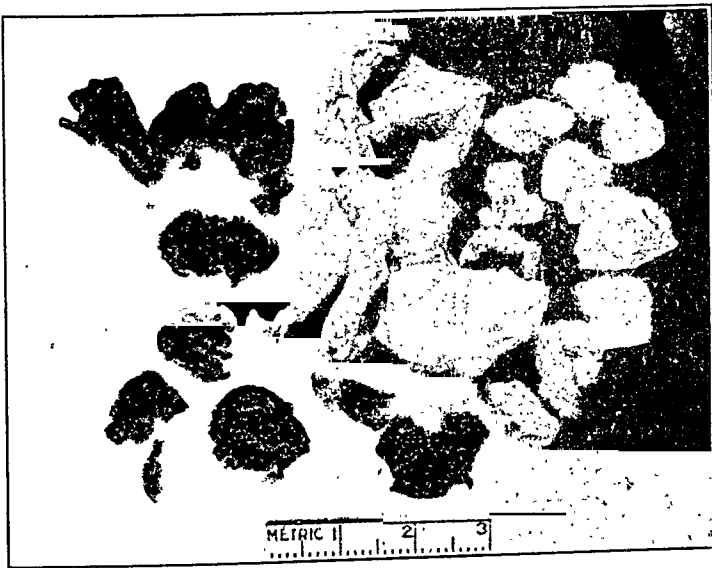


Fig. 1.—Multiple adenomyomas.

that the uterus be removed. At operation, multiple endometrial growths were removed and presacral resection was performed. This was followed by complete relief of pain and by normal menstruation.

Fixation of the uterosacral ligaments and rectovaginal septum usually results in pain of a bearing-down type and, in some cases, in a desire to defecate. These symptoms begin before menstruation is initiated and abate somewhat after the onset; in many cases, however, a dull aching pain is present after the flow ceases. As the disease progresses the duration of the pain increases, so that in the most severe cases patients may not be free from discomfort at any time. Patients presenting such a history usually require radical surgical treatment. In our recent series of 308 cases, in which the data are more complete, 46.8 per cent of the patients had dysmenorrhea, of whom 39.6 per cent had increasing pain and 24 per cent of the entire group had had no pain (Table III). Keene and Kimbrough found that 49.1 per cent of their patients gave a history of increasing dysmenorrhea and that 40 per cent gave no history of pain. Donald has stated that acquired dysmenorrhea was noted in 50 per cent of his cases. It was of interest that 18.7 per cent of our patients with menstrual pain volunteered the information that this pain was definitely worse on exertion. This seemed to be significant since it occurred in cases of extensive involvement.

in cases of chronic inflammatory lesions, especially if the examination is made near the beginning of menstruation. If nodules are also felt behind the cervix or in the posterior vaginal vault, the diagnosis of endometriosis is more nearly certain.

Palpation of the uterosacral ligaments by rectal examination is of distinct value, because they are usually shortened irregularly and are extremely tender. The induration of pelvic inflammatory disease, particularly of the postabortal type, is firmer and more extensive than is encountered in endometriosis.

In the presence of large leiomyomas and tarry cysts, the diagnosis of endometriosis is more difficult to make. In the case of young patients without uterine tumors but with fixed retroversion associated with an increasing dysmenorrhea and without a history of acute pelvic infection, there is presumptive evidence of endometriosis.

As has been said, very little evidence of the presence of endometriosis can be obtained from the character of the menstrual disturbance in view of the fact that such disturbances can be more accurately attributed to an associated uterine or ovarian lesion. Further proof of this lies in the fact that most patients with endometriosis but without associated uterine lesions do not have menstrual irregularities. In our recent series of 308 cases a preoperative diagnosis of endometriosis was made in forty-five instances.

TREATMENT

Since the epochal work of Sampson and of the many others who have investigated the disease thoroughly, it is definitely established that the syndrome produced by endometriosis is dependent on ovarian function. A rather general rule can therefore be stated that removal of ovarian function will cause these lesions to become quiescent and in some instances to disappear. A few exceptions might be made, however, in the case of adenomyomas of the uterus following the menopause. Other factors producing activity of such adenomyomas may be accounted for by malignant ovarian tissue.

Since in most cases endometriosis occurs during the reproductive period, conservative surgical principles with regard to preservation of either the menstrual or reproductive function, or both, must be employed. We at the clinic feel that the upper age limit for conservative procedures is between 37 and 40 years. However, the extent of the lesions and their location are of more importance in selecting the type of operation perhaps than is the age of the patient. For example, if a patient at the age of thirty has a diffuse endometriosis involving the sigmoid, both adnexa and the uterus, she will be better off if a radical operation is performed.

It has been our observation that when it is necessary to perform radical hysterectomy for endometriosis before the menopause, the patients do not experience the severe menopausal symptoms that those patients do who undergo a similar operation for conditions other than endometriosis.

Conservative methods carry a more favorable prognosis when lesions are confined to the adnexa on one side and to a few serosal implants which can be easily excised. In the cases of younger patients with a longer history of dysmenorrhea and in which endometriosis is encountered at operation we have, in addition to conservative treatment, performed presacral resection with the idea in mind that if there were recurrences the patients might not experience the dysmenorrhea which was the original predominating symptom. By this means such patients might carry on in comparative comfort until later in life or until further symptoms justified destruction of ovarian function by surgical means or by irradiation.

In our combined series of 884 cases, 162 patients were treated by conservative procedures, 701 by radical procedures, and a few by radium and roentgen rays (Table VI). When the lesions were diffuse, and particularly when there was considerable fixation of the lower uterine segment, even though the adnexa were not extensively involved, it was our opinion that the risk of recurrence following any conservative procedure was too great. Those patients who had involvement of the rectovaginal septum were treated in the great majority of instances by radium, be-

well be an etiologic factor in the subsequent production of endometriosis in the pelvic structures. In our recent series of 308 cases, 167 patients (54.2 per cent) had been subjected to previous pelvic operations, but it was not possible to determine in many instances the reason for the operation. Of these, 56.9 per cent underwent some type of surgical procedure on the uterus or adnexa, 12.6 per cent had had dilatation and curettage and perineal surgery, and 30.5 per cent had undergone appendectomy or some other abdominal operation. Whether these procedures were performed for pelvic pain or whether they may have been one of the factors in initiating the endometrial process is impossible to say. The high incidence of previous surgical interference, however, is certainly suggestive (Table V).

TABLE V. PREVIOUS SURGICAL PROCEDURES: 308 PATIENTS
(RECENT SERIES 1935-1937)

	NUMBER	PER CENT
Previous surgical treatment	167	54.2
Involving cutting uterus, tube, or ovary	95	56.9*
Dilatation and curettage and perineal surgery	21	12.6*
Appendectomy or other abdominal surgery	51	30.5*
No previous surgical treatment	114	37.0
No information	27	8.8
Total	308	

*Per cent of 167 patients who had had previous surgical treatment.

DIAGNOSIS

The clinical diagnosis of endometrial lesions is rarely made in more than 20 per cent of the cases because of the multiplicity of associated pathologic lesions of the uterus and ovary which may themselves account for the patient's symptoms. There are certain symptoms, however, which, if present, should direct attention to the possibility of endometriosis even though associated lesions are present; for example, an acquired dysmenorrhea of the progressive type occurring in a woman particularly between the ages of 25 and 45. This pain will vary in character depending on the site of the lesion. Adenomyomas of the uterus not infrequently extend through and involve the posterior wall of the bladder, giving rise to vesical symptoms associated with menstruation. This experience will usually be mentioned by the patient without any leading questions by the examiner. Similarly, adenomas involving the cul-de-sac or rectal shelf are usually productive of such rectal disturbances as pain on defecation or rectal pressure, both of which seem to be definitely associated with the initiation of menstruation. In cases of diffuse involvement of the pelvic tissues and rectal shelf, there is a characteristic discomfort which I have not seen mentioned by previous authors; this is pelvic "soreness" brought about by exertion near or during menstruation. It is especially noticeable on walking or riding in such vehicles as buses, streetcars, or automobiles for any considerable distance. When patients complain of sterility and have rather pronounced dysmenorrhea, endometriosis should be excluded.

Endometriosis of the umbilicus presents very little difficulty in diagnosis, such lesions being characterized by their tenderness, enlargement, and discoloration at the menstrual periods. The same is true of lesions in laparotomy scars, particularly following cesarean section, although in the latter instance a sinus may discharge blood coincidentally with menstruation. There may be periodic discharges of blood from the umbilicus of patients who have not had previous operations. Keene and Kimbrough called our attention to a very important point in connection with bloody discharging sinuses subsequent to operations on the uterus: The sinus may connect directly with the uterine cavity, from which blood may be discharged, without the presence of an endometrioma.

Objective evidence of endometriosis is best ascertained through bimanual examination. The most positive evidence is the detection of small nodules in the cul-de-sac on rectal examination. Tenderness is usually out of all proportion to that seen

TABLE VIII. FERTILITY: 162 PATIENTS TREATED CONSERVATIVELY

	NUMBER	PER CENT
Unmarried	31	19.1*
Married	131	80.9
No pregnancy	42	32.1†
One live birth	18	13.7
Two or more live births	34	26.0
Miscarriages only	22	16.8
No information	15	11.4

*Based on 162 patients.

†Based on 131 married patients.

tion impresses us as being of more value in cases in which we can subsequently follow the patients with regard to fertility than for the entire group, the majority of whom underwent radical operation.

Thirty-one of these 162 patients were unmarried, 131 were married. Our figures for fertility are accordingly based on these 131 patients in whom one could expect pregnancy under normal conditions. In this group there was no pregnancy, or an absolute sterility in 42 cases, or 32.1 per cent; 18 patients or 3.7 per cent, had 1 live birth, 34, or 26 per cent, had 2 or more living births, and 22, or 16.8 per cent, had only miscarriages. We were unable to obtain information in 15 cases, or 11.4 per cent. The incidence of pregnancy, therefore, for this group was 56.5 per cent. The incidence of miscarriage was extremely high, which is presumptive evidence that endometriosis is a very potent factor in it.

Seven patients were known to have become pregnant after such conservative treatment. Of these, 4 had 1 child each, 1 had 2 children, 1 had 4 children, and 1 had a miscarriage, giving a total of 10 children. It should be noted, however, that of the 162 patients who were treated conservatively, 64 were not traced in respect to subsequent pregnancies, 10 were more than 40 years of age at the time of operation, 18 were unmarried, and 15 were sterilized by operation, so that in only about 55 cases could one reasonably expect a report of pregnancy.

RESULTS OF CONSERVATIVE SURGICAL TREATMENT

In evaluating the results obtained from conservative treatment one must consider the degree of pelvic comfort obtained, whether normal menstruation was continued, and in the cases of those who were married and desired pregnancy, whether this function was improved. When conservative measures were carried out, it is to be inferred that the disease was not extensive and that the patient probably sought treatment for dysmenorrhea or to inquire about sterility.

In order to alleviate the dysmenorrhea, we have in addition to local excision been performing presacral resection. This latter was carried out in 13 of the cases in which local excision was performed. In 5 cases in which unilateral oophorectomy, and in one case in which bilateral salpingectomy was performed, a presacral resection was also carried out. We were able to trace 13 of these patients (Table IX).

TABLE IX. RESULTS: 162 PATIENTS TREATED CONSERVATIVELY

	TREATED	TRACED	IMPROVED, GRADE 1-2	IMPROVED, GRADE 3-4	UNIMPROVED	SUBSEQUENT PREGNANCY	SUBSEQUENT OPERATION	SUBSEQUENT RADIUM R _x	SUBSEQUENT X-RAY R _x	DEATHS
With presacral resection	19	13	3	6	3	4				
Without presacral resection	143	85	16	48	20	3	4*	1	2	1
Total	162	98	19	54	23	7	4	1	2	1

*Freeing of adhesions and oophorectomy in 1 case; panhysterectomy in 3 cases.

TABLE VI. ENDOMETRIOSIS: 1923-1937, 884 PATIENTS

TREATMENT	NUMBER	PER CENT OF CASES
Conservative:*		
With presacral resection	19	2.2
Without presacral resection	143	16.2
Radical	701	79.3
Radium	17	1.9
Roentgen	2	0.2
Roentgen and radium	2	0.2
Total	884	100.0

*Operations conserving menstrual function.

cause the surgical risk of excising this particular lesion is too high when it is considered that such patients can be treated satisfactorily by destroying ovarian function by radium. In two instances in which there was a definite history of post-abortual infection, roentgen therapy was employed.

Of the total of 162 conservative surgical procedures in addition to local excision, a tubal operation was employed in 9 cases, oophorectomy alone in 19, salpingo-oophorectomy in 51, local excision in 77, and bowel resection in 6, with or without uterine suspension and with or without presacral resection. Myomectomy was performed in 26 cases (Table VII). This group of 162 patients comprises only 18.4

TABLE VII. SURGICAL PROCEDURES IN 162 CASES IN WHICH PATIENTS WERE TREATED CONSERVATIVELY

PROCEDURE	TOTAL		UTERINE SUSPENSION				WITH PRESACRAL RESECTION	
			WITH		WITHOUT		NO.	%
	NO.	%	NO.	%	NO.	%		
Tubal operation	9	5.6	4	8.7	4	4.1	1	5.3
Oophorectomy	19	11.7	8	17.4	6	6.2	5	26.3
Salpingo-oophorectomy	51	31.5	14	30.4	37	38.1		
Local excision*	77	47.5	20	43.5	44	45.4	13	68.4
Bowel resection	6	3.7			6	6.2		
Total	162†	100.0	46	100.0	97	100.0	19	100.0

*Local excision of endometrial tissue only. In the cases of the other surgical procedures listed, there was also excision of endometrial tissue.

†Myomectomy, which was performed in 28 cases, is not listed in this table.

per cent of the total, which indicates that we have been more radical in our surgical management of the disease than is shown by the report of previous authors. Our selection of cases for conservative management, however, seems justified by the fact that we have had only a small number in which it was necessary to submit the patients to secondary surgical procedures or to radium therapy. Further justification lies in the fact that patients who have already undergone previous pelvic operations, of which there were 167, were unwilling to assume the risk of recurrence. The average age of the group of patients treated conservatively was 33.8 years.

The question of fertility in endometriosis is of considerable importance. It is our observation that if the disease has existed over a long period, and if the symptoms are severe, the possibility of subsequent pregnancy should be quite remote. In the cases of those patients with secondary sterility, the onset of the disease frequently dates back a short time subsequent to delivery, giving cause to believe that the pregnancy or delivery may have been an exciting factor in its production or that the pregnancy or delivery may have reactivated a pre-existing endometriosis. Our information with regard to fertility is derived from the cases of the 162 patients who were treated conservatively and about whom we have fairly accurate information both before and after the pelvic operation (Table VIII). This informa-

procedures will be required to remove the disease. I believe it is safer to err on the side of radicalism than to attempt preservation of ovarian function in those cases in which there is some involvement of both adnexa or in which there is considerable involvement of one adnexa and the adjacent uterine wall.

Conservative procedures cannot be recommended for the elimination of sterility, although they should be carried out whenever possible in the hope that fertility may be restored during the reproductive period of life.

Attempts to relieve dysmenorrhea by resection of the presacral nerves would seem to be definitely indicated as an adjunct to conservative surgical treatment in the hope that distress from later recurrences may be greatly minimized. Such relief of menstrual pain may also have some effect on the restoration of fertility, although with the evidence at hand presacral resection cannot be advocated as a method of restoring this function.

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DISCUSSION

DR. FRANK A. PEMBERTON, BOSTON, MASS.—At the Free Hospital for Women we have had 470 cases of endometriosis up to 1936 proved by pathologic examination. Thirty per cent had conservative operations as against 18 per cent in Dr. Counsellor's series, but in the last 100 cases there were only 12 conservative operations. There was only one death from embolism in our series which is interesting because many of the operations are difficult on account of the tough adhesions.

As regards the principal sites of the disease, both ovaries were concerned in 158, the left ovary in 133, and the right ovary in 89. The ovaries were not involved in 13 per cent of the cases, a fact which has been reported before but is not generally realized.

Of the patients treated by conservative operation, we could not follow 31. Eighty per cent required no further treatment. Further treatment of the remaining 20 per cent consisted of conservative operations in two cases, radical operation in 16, radium in 1. The x-ray has a decided place when conservative treatment fails, for with it the tumors will disappear.

Of the 83 patients who were under forty and were married 16 became pregnant once after the operation; one became pregnant twice. An interesting point is that of these 16 only 3 have needed radical operation since the pregnancy. Most of the pregnancies occurred within the first two years, so that it appears that if these patients do not become pregnant within that time they are not likely to do so. This is perhaps one reason for not doing conservative operations, for there is little point in doing an operation so that the patient may have just one more child if she already has some.

Nearly 6 per cent of these patients showed associated proliferating tumors of the ovaries. Seven of these were malignant.

The amount of relief from pain obtained by 3 of them was Graded 1 to 2, on the basis of 4, and by 6 was Graded 3 to 4; three patients were not improved. Four, or 21 per cent of those who underwent presacral resection, however, became pregnant subsequently. This may indicate that pain, if not relieved, militates against pregnancy. This number of cases is too small, however, to draw any definite conclusions. With regard to pain, approximately 70 per cent of the patients received sufficient relief, so that it was not necessary to subject them to subsequent treatment.

In the remaining 143 cases of this group of 162, presacral resection was not performed. Eighty-five of these patients were traced. Sixteen obtained moderate improvement (Grade 1 to 2), whereas 48 obtained practically complete relief from pain (Grade 3 to 4). Approximately 75 per cent, therefore, were relieved of the pain for which they sought treatment. Twenty patients in this group were unimproved. In 7 of the cases it was necessary to apply subsequent treatment; in one case secondary oophorectomy and freeing of adhesions were carried out, and in 3 cases panhysterectomy was performed. Ovarian function was terminated by the use of radium in one case, and in two cases in which secondary pelvic inflammatory infection was suspected roentgen therapy was employed. One patient of the series died of peritonitis secondary to partial resection of an endometrial growth constricting the sigmoid. It is interesting to note that all the patients whom it was necessary to treat subsequently by irradiation or surgery were in this group in which presacral resection was not carried out. This in a way substantiates our belief that presacral resection may be of considerable value in preventing later surgical treatment even though lesions may recur.

It is not possible to show that conservative procedures for sterility are of much value since only 7 of the 55 patients whom one could reasonably expect to become pregnant did subsequently become so. However, these 7 pregnancies resulted in 10 living children. It seems to us that pregnancy can be expected only in those cases in which the disease is limited to one adnexa or to a relatively few implants which can be excised, such as we encountered in the group of cases in which presacral resection was performed.

The majority of patients who underwent presacral resection menstruated in small amounts within the first few days following operation even though it was not the regular time for menstruation. What produces this uterine bleeding is not clearly understood, but we rather suspect that it accompanies profound relaxation of the myometrium and is not due to any effect on the ovary. Menstruation in these cases remained normal, with regard to periodicity, duration, and amount of flow, as it has also in all of the other cases in which patients were treated conservatively without presacral resection. It would appear that normal menstrual function can therefore be reasonably expected in cases of limited extension of this disease, although the reproductive function may be faulty.

SUMMARY AND CONCLUSIONS

Endometriosis is an extremely important disease of young women, and its most predominant symptom is dysmenorrhea of an acquired or progressive type. Vesical and rectal pain superimposed on dysmenorrhea is almost always diagnostic. Diffuse pelvic soreness, brought about by walking or jarring of the pelvis in any way, is also suggestive.

In the majority of cases, endometriosis and its associated lesions of the uterus and adnexa will require radical surgical treatment. Radical treatment was carried out in 79.3 per cent of the present series of 84 cases.

Cases in which conservative procedures are to be carried out must be very carefully selected if recurring lesions and subsequent treatment are to be avoided. The percentage of recurrences will be reduced by limiting conservative treatment to those in which relatively few surgical

We are not sure about these cases, of course, but it is suggested that they may be endometriosis of the lung. It was discussed whether such a growth could take place in the lung and the surgeons whom we consulted felt that such a thing was not possible. I pointed out that Allen had previously demonstrated the growth of endometrial tissue in the anterior chamber of the eye, and I felt that there was no reason why it could not grow in the lung. I suggested to my associate, Dr. Hobbs, that he take some rabbits, give them theelol and remove the uterus, make a return emulsion of the endometrium and inject it in the rabbits' ear veins. This was done in ten animals, the animals sacrificed in eight weeks, and we believe endometrial proliferation has been demonstrated. I think those who are working with lung tumors should keep this in mind. The work of Dr. Hobbs will be published shortly.

DR. WILLARD R. COOKE, GALVESTON, TEXAS.—I should like to ask Dr. Counsellor whether he has observed any spontaneous disappearance of massive endometriosis following conservative operations? We have had five cases, in which as much as possible of the mass was removed without destruction of the ovary, and presacral sympathectomy and ovarian neurotomy were performed. In all but one there was a complete subsequent disappearance of the masses. In the one exception there is still a small nodule in the right uterosacral ligament.

We should follow these patients as closely as we do our carcinoma patients, particularly those who have had presacral resection. We have found in a small series that operative castration gives the best results, radium treatment next, and x-ray therapy last.

DR. N. SPROAT HEANEY, CHICAGO, ILL.—I take a conservative attitude toward these cases, often going to an elaborate dissection in order to preserve ovarian function, feeling that in the event of failure the x-ray is always at hand to prevent a second operation. Frequently, multiple small areas can be well attended to by the use of the nasal cautery where dissection with the knife would be difficult. We should keep in mind always the factors of etiology in the treatment of these cases. Constrictions of the cervix should be done away with and retrodisplacements should be corrected.

There were only 14 with the rectosigmoid or vaginal septum affected. Only one of these needed treatment, a colostomy being done. She also had a hysterectomy with removal of the ovaries, and in six months the tumor in the intestine had atrophied, the bowels moved normally, and the colostomy closed.

DR. RAYMOND E. WATKINS, PORTLAND, ORE.—Early recognition of this disease seems to us of considerable importance. From the observations we have made of 15 patients with early ectopic endometriosis, 14 have had poorly developed retrocessed uteri. It was also noticed that where these early growths had occurred the body of the uterus was sharply flexed on the cervix either forward or backward. We believe that varying amounts of retrograde menstruation frequently occur in the presence of such uteri, the quantity depending on the amount of obstruction offered by the flexion in the cervix and the degree of patency of the Fallopian tube. The probable chemical irritation of the cul-de-sac is caused by such menstrual fluid.

This patient with retrodisplacement was operated upon on the third day of her menstruation. The menstrual fluid was present in her cul-de-sac and the filmy adhesions had occurred, denoting a low grade inflammatory condition. There was no history or evidence of previous pelvic infective inflammatory disease in this patient. The contents of the cul-de-sac were aspirated (20 c.c.), later centrifuged and microscopic sections showed a strip of endometrial cells which had escaped into the cul-de-sac. However, no gross evidence of endometriosis was found in this case. Such a chronic inflammatory process as seemingly produced by the monthly escape of menstrual fluid in this patient would seem to prepare the field for the reception of either transplants of cells or invite metaplasia. Dr. Sampson found such retrograde flow and cells in the cul-de-sac.

When the lesions are small and few in number, they may be excised, but frequently the patches are too scattered for excision. In such instances we have used the small cervical type of cautery to destroy them. In addition to the destruction of such early lesions, surgical replacement of the uterus would seem advisable in all cases. Following this type of therapy we have had satisfactory operative results in the majority of instances, our patients being relieved of the pain and discomfort from which they suffered before.

In the group of 15 patients referred to, the average age was 25. All had dysmenorrhea becoming progressively worse. Five of 9 married women complained of dyspareunia, stating that pain occurred in the upper vagina. Ten had associated sacral backache at menstrual time. Six had rectal pain at menstrual time. Fourteen of the 15 had retrodisplaced uteri. Twelve had unusual tenderness of the cul-de-sac on vaginal examination. Seven showed a nodular or beady condition of the uterosacral ligaments on rectovaginal examination.

DR. OTTO H. SCHWARZ, ST. LOUIS, MO.—I was interested in the distribution of the lesions in Dr. Counsellor's series and noticed that there were none outside of the pelvis. Also there was only one lesion of the appendix, none of the abdominal scar. In a very much smaller series we have had three lesions in the abdominal scar and seven in the appendix.

This brings up the question of distant lesions of endometriosis. In the recent German literature there are two cases described, one of endometriosis on the anterior aspect of the thigh and another in the forearm. The only way that I can possibly conceive of these occurring is that they must get there through the arterial system. Sampson has shown that endometrial fragments are seen very frequently in the veins of the broad ligaments, but he has not described them in vessels outside.

We had an interesting experience in St. Louis with two cases. One woman had a definite inguinal gland endometriosis and a lung tumor which bled at each menstrual period. X-ray showed this tumor. No biopsy of course could be obtained. The ovaries were x-rayed and since that time she has had no more bleeding from the lungs. In a similar case a lung tumor was x-rayed, but biopsy failed to reveal anything.

As a result of these unfortunate experiences, we undertook to develop a medium which would be nonirritating and also quickly resorbed and excreted. A preliminary report of our work was published in 1937.⁴

Mono-iodomethane sulphonate of sodium (skiodan) is an organic compound containing 52 per cent of iodine in stable combination. In aqueous solution it has been used extensively by urologists. Its injection intravenously for excretion urography and its direct injection

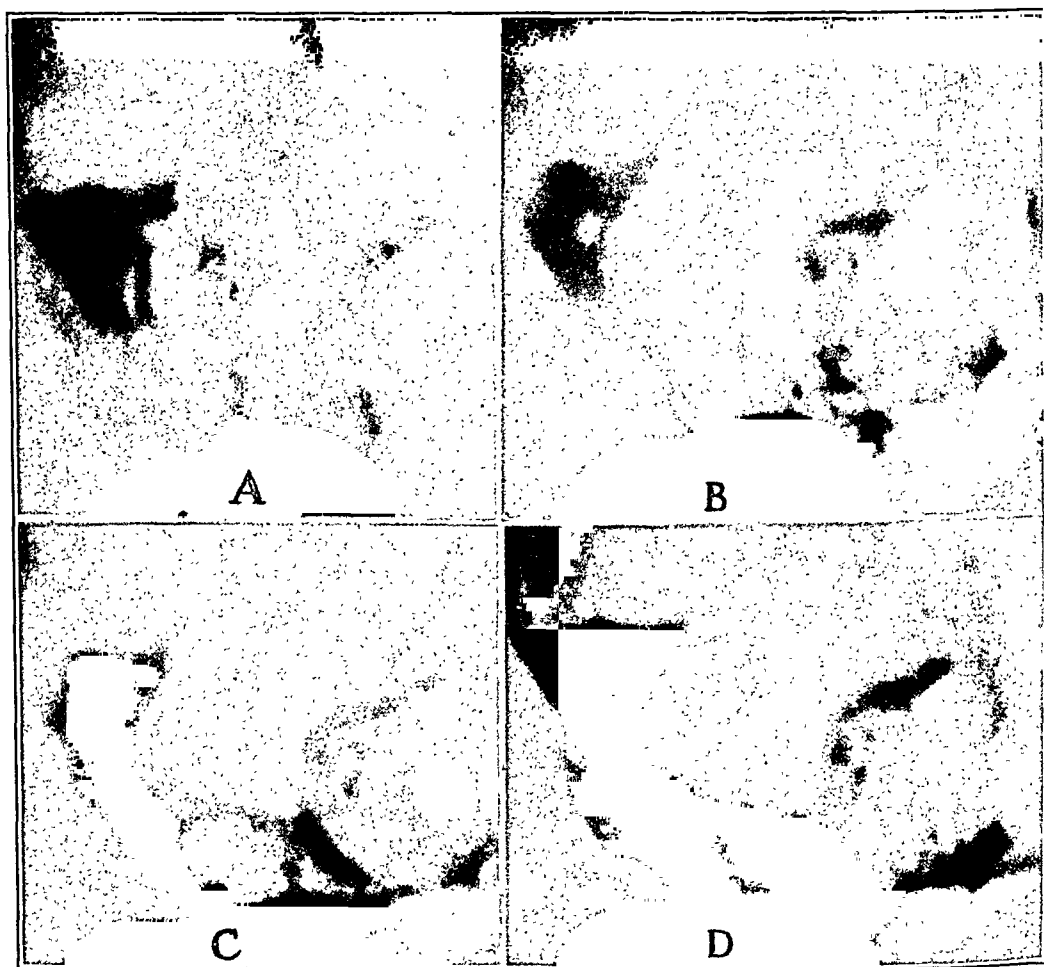


Fig. 1.—Serial uterosalpingograms (Hyams' technic) using 2, 4, 6, and 8 c.c., respectively, of skiodan-acacia solution. A and B show filling defects in uterine cavity due to polyps, not visible in C and D, being obscured by further distention. Left tube is patent, and right tube occluded with displacement of uterus toward right (probably adhesions).

into the urinary passages for retrograde pyelography show it to be free from local irritative or generalized reactions, and in other instances direct injection into the arteries for arteriography has not been attended by untoward effects. In experimental animals after the injection of large amounts of this preparation no free iodine or inorganic iodine could be detected in the blood or urine, so that iodism may be considered as virtually impossible following its use. Moreover it is rapidly excreted. When injected intravenously into rabbits,

A NEW, NONIRRITATING OPAQUE MEDIUM FOR UTEROSALPINGOGRAPHY*

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THE injection of an opaque medium into the uterus and Fallopian tubes for the purpose of x-ray visualization, suggested by Cary¹ and independently by Rubin² in 1914, is with certain limitations a valuable diagnostic procedure.

In sterility studies in our clinic this procedure has been used only as an adjunct to the Rubin insufflation with carbon dioxide gas. This latter test is entirely sufficient to demonstrate patency of the tubes, is safer and simpler, and also is considerably less expensive for the patient than x-ray examinations. We resort to uterosalpingography only when tubal obstruction is demonstrated by the Rubin test, or when small tumors or polyps of the uterus are suspected.

Proper technic of injection of an opaque medium will usually locate fairly accurately the site of a tubal obstruction, or the presence of small new growths. By proper technic, we refer to the method recommended by Hyams³ which consists in the injection of fractional doses of 2 c.c. each of the medium, an x-ray film being exposed after each such dose until a series of five pictures have been made, or fewer if the patient complains unduly of pain. The maximum capacity of the uterus and tubes is about 10 c.c., and more than this may be harmful, especially if obstruction exists. This fractional or serial method has many diagnostic advantages over that of a single large injection with only one or at the most two x-ray pictures.

Even with this careful technic, which effectually prevents overdistention of these cavities, and even with the limitation of uterosalpingography to cases in which it is clearly indicated, untoward reactions occur all too frequently. We have had several instances of acute "chemical" salpingitis, parametritic masses, and occasional allergic reactions following the use of iodine in oil. The liberation of free iodine from these solutions has been thought by us to be the cause of some of these reactions. Late or delayed reactions are probably due to the foreign body effect of oil on the peritoneum, and many instances of encysted oil in the peritoneal cavity have been reported in the literature. The persistent presence of iodized oil can be demonstrated by x-ray examination days or weeks after its injection.

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

iodomethane sulphonate of sodium (40 per cent) with acacia (20 per cent) which finally solved this problem admirably.

The suggestion has been made that because acacia solution injected intravenously in copious amounts has proved dangerous in some in-

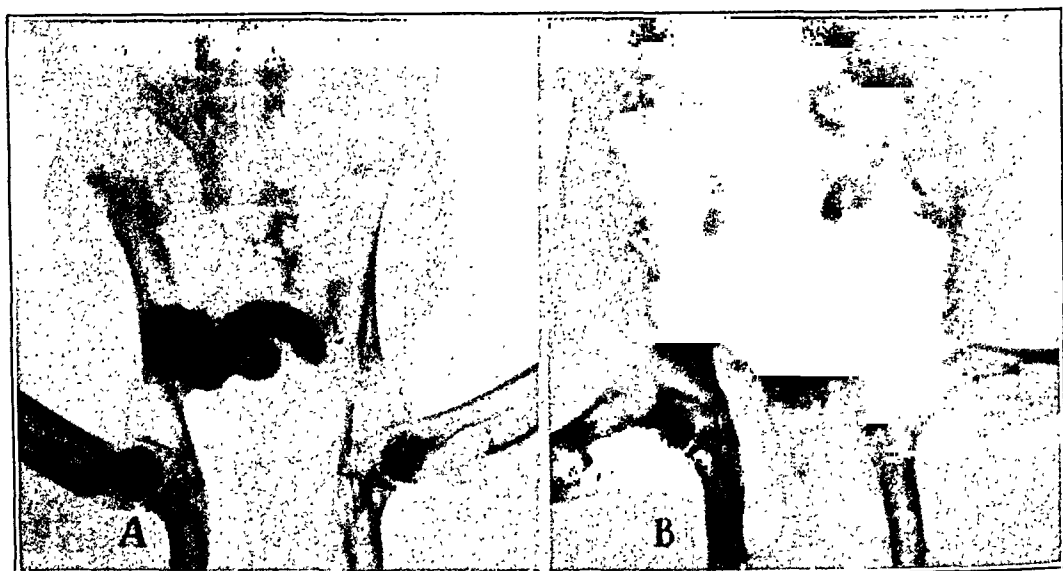


Fig. 3.—Rate of resorption shown by x-ray. *A*, Shows ligated horn of rabbit uterus thirteen minutes after injection with skiodan-acacia; *B*, shows same rabbit ninety-three minutes after injection, shadow now appearing in urinary bladder as skiodan-acacia is taken up from tube and is being excreted in urine.

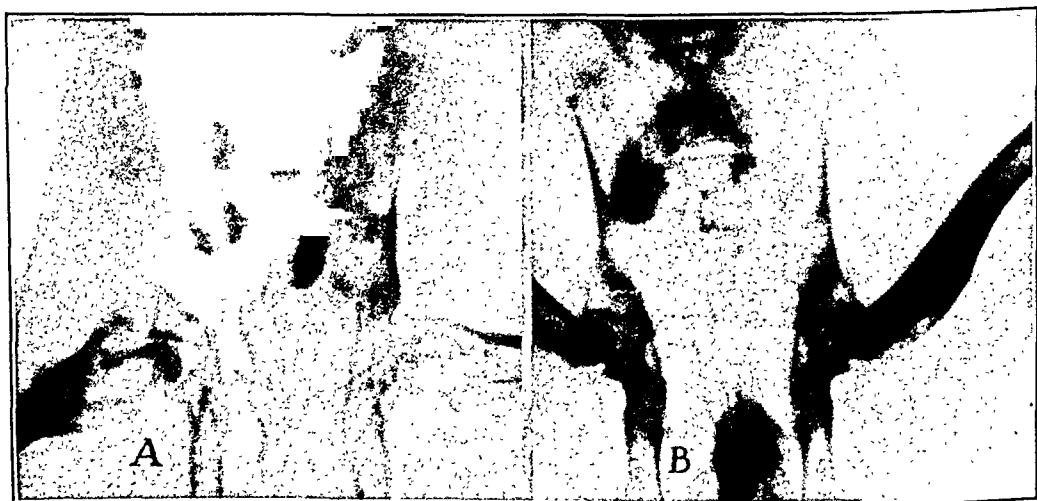


Fig. 4.—Similar to Fig. 3. Another rabbit, *A*, showing uterine shadow immediately after injection; *B*, showing fading of uterine shadow and formation of bladder shadow thirty-five minutes after injection.

stances, its intrauterine use might be similarly undesirable. It must be remembered however that only 10 c.c. are injected, and these into the uterus, not into a vein. If a blood vessel were invaded accidentally the amount received into the circulation would be so small that it could not, conceivably, cause harm.

the rate of excretion is approximately 47 per cent in one hour, 76 per cent in three hours, and 89 per cent in nine hours. The rate of excretion in man (normal kidneys) is even faster.

We found that the aqueous solution of this substance was unsuitable for uterosalpingography because of its lack of viscosity. Even a small amount of the watery solution spurted through the uterine cavity and the tubes because it was so fluid. As a result of this these x-ray pictures were uniformly unsatisfactory. Consequently an attempt was made to thicken the preparation so that its chemical con-

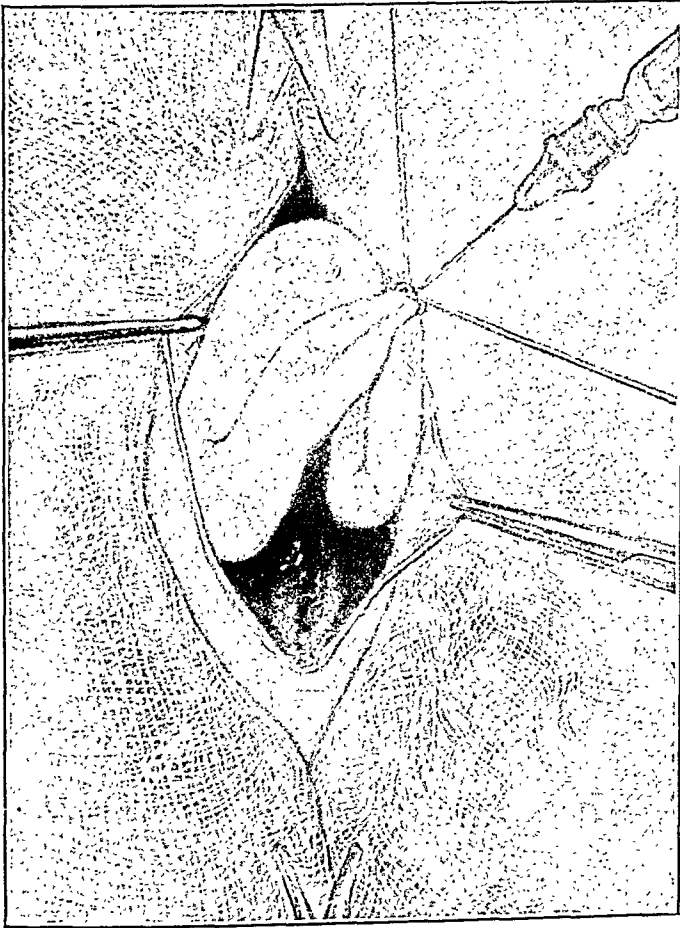


Fig. 2.—Technic of direct injection into one horn of rabbit uterus. The lower portion is ligated to prevent leakage through cervix, and opposite horn is used as normal control during subsequent histologic search for evidence of inflammatory or irritative reaction.

tent would remain the same as that already found suitable for x-ray visualization in urologic work, while its viscosity would be approximately the same as that of the more familiar iodized oil.

It is not necessary to recount here the details of the tedious and sometimes discouraging series of preparations made and discarded. Glucose, propylene glycol, starch, tragacanth, and other similar thickening mediums were tried and by animal experimentation found unsatisfactory. Dr. O. W. Barlow of the Winthrop Chemical Company's Research Laboratory suggested and prepared a mixture of the mono-

1. *Local Irritative Effects.*—The female rabbit exhibits the extremest manifestation of bifid uterus, possessing two separate and complete uteri, each with its individual cervix in the vault of the vagina. This permits the isolation of a substance introduced into one of the uterine horns, preserving the other for control.

Rabbits were treated by injecting 1 c.c. quantities of sterile skiodan-acacia into one intact horn of the uterus. A curved metallic catheter was inserted through the vestibulum so that its tip was well up into the vagina. A ureteral catheter, threaded through the metallic one, was guided past one of the cervixes of the double uterus into the lumen of the uterine horn by careful manipulation of the intact genitalia through an abdominal incision. The skiodan-acacia was injected through the fine catheter by means of an attached syringe. The catheters were then withdrawn and the incision closed.

These rabbits were examined by biopsy forty-eight hours to so long as seventy-nine days after injection. The gross condition of the genitalia and peritoneum was noted, and specimens of both uterine horns removed for microscopic examination.

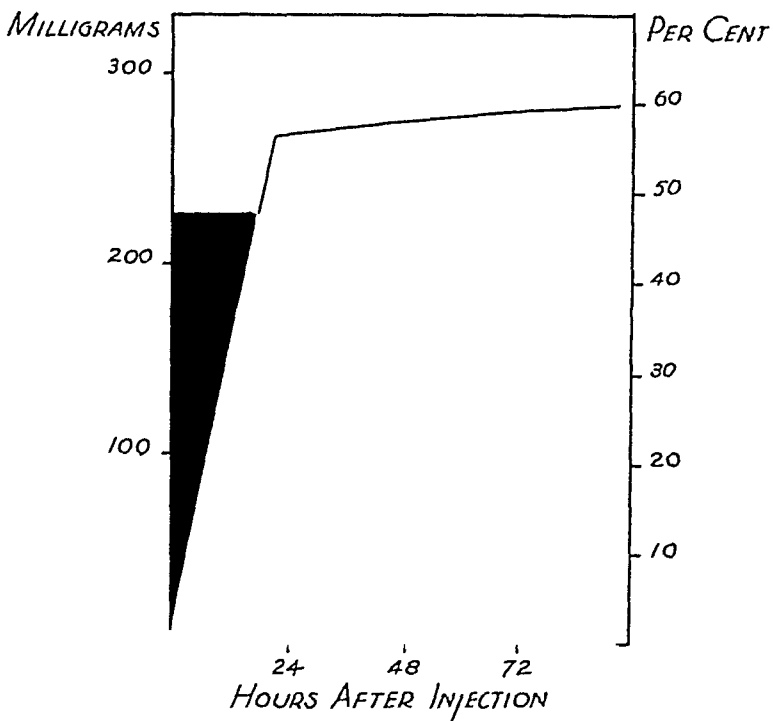


Fig. 6.—Skiodan-acacia (400 mg.) injected directly into peritoneal cavity (compare with Fig. 5).

No more pathologic change could be observed on gross or microscopic examination than would be expected from the forcible distention to which the uterus was subjected.

The effect of skiodan-acacia on the Fallopian tubes of rabbits was next studied.

The uterus was exposed by a low midline incision, and a hypodermic needle inserted distally through the wall and into the lumen of one uterine horn. A ligature was passed around the horn and needle. After injection of the predetermined amount of fluid, the ligature was tightened as the needle was withdrawn so that the fluid could not pass into the vagina, or into the peritoneal cavity through the needle puncture.

At the end of forty-eight to seventy-two hours, biopsies were performed, and specimens from the uteri and tubes fixed for microscopic examination. In spite of the fact that the treated uterine horns were found uniformly to be distended with fluid on biopsy, no more evidence of specific irritant effect on the uteri could be observed than could be accounted for by mechanical distention. No microscopic difference was seen between the treated and untreated Fallopian tubes.

We have carried out extensive experimental investigations in the Oliver Research Laboratory at our Hospital to determine any possible harmful and irritative effects of this new preparation, and independently, similar and elaborate studies have been made by Dr. Barlow in the Winthrop Research Laboratories. After satisfying ourselves that such effects were lacking in animals we began its clinical use in the hospital.

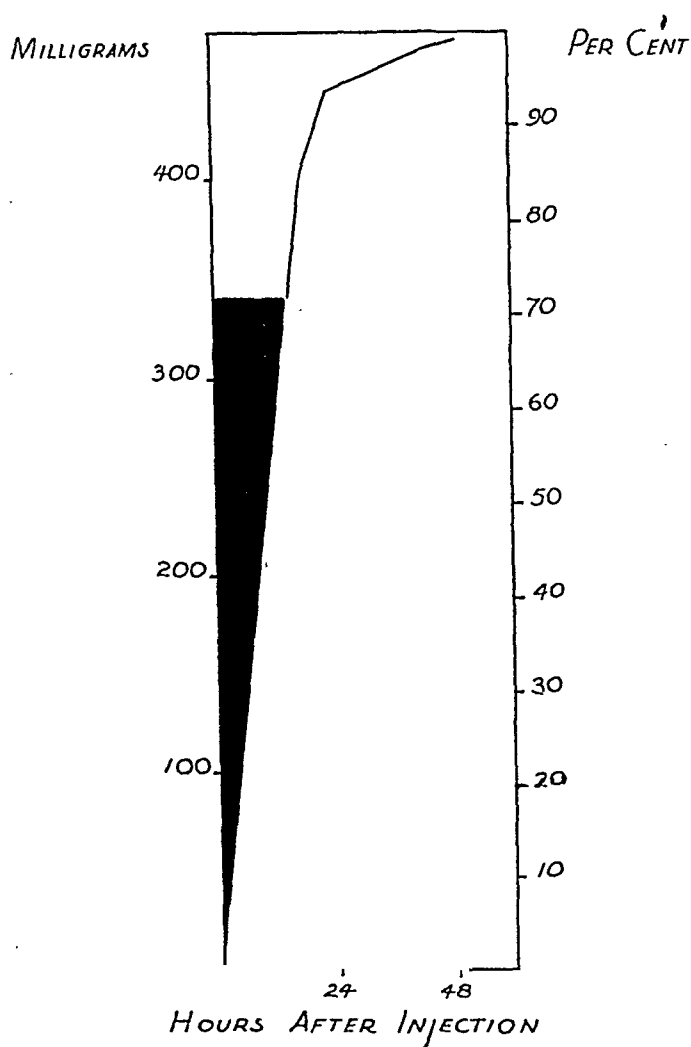


Fig. 5.—Rate of elimination shown by chemical analysis. Skiodan-acacia (400 mg.) injected into doubly ligated uterine horn. Vertical bars indicate milligrams of iodine compound in urine; line, total elimination, percentage of amount injected.

SUMMARY OF EXPERIMENTS

Our preliminary experiments fall into three parts: First, an attempt to determine any local inflammatory effect from the introduction of the radiopaque compound into the female genitalia or peritoneum of rabbits; second, a study of the resorption of the compound after its injection into the uterus, and its excretion by the kidneys as shown by x-ray films; and third, the study of the speed of resorption and elimination by the kidneys, by means of chemical analyses.

From the experiments on urinary excretion as well as from the x-ray studies, it is apparent that skiodan is rapidly absorbed from the uterus, and from the peritoneum, and the greater part excreted by the kidneys within eighteen hours. Whether or not iodized oil could be eliminated as readily from the rabbit's body, if anuria did not follow its administration, cannot be definitely decided from our experience. It seems unlikely, considering the lipoid nature of the material.

CLINICAL APPLICATION

Our clinical results from the use of this nonirritating radiopaque substance have been uniformly satisfactory. In a fairly large series of patients there have been no evidences of inflammatory reactions, either immediate or delayed. Moreover, the x-ray pictures seem sharper and clearer than with the iodized oil preparations.

X-ray pictures taken within a few hours after the original clinical diagnostic series show that the radiopaque substance has entirely disappeared.

Further investigations are being undertaken in our Research Laboratory to determine the actual rate of excretion of the compound through the urine of these patients. Another study is being projected to determine the ultimate fate of the acacia thus injected. This appears to be excreted through the bowels.

SUMMARY

1. Uterosalphingography, as an adjunct to transuterine tubal insufflation in sterility studies, is a useful diagnostic measure in a certain restricted group of case instances.

2. Iodized oil injected into the uterine cavity and the Fallopian tubes as the opaque medium for x-ray visualization is followed too frequently by sharp reactions, either from chemical irritation by the iodine, or allergic in type as though from the oils.

The foreign-body effects of iodized oil, persisting as this substance does for indefinite periods of time after injection into the abdominal cavity, result often in encysted masses with local acute and chronic peritonitis.

3. In an effort to avoid such reactions, a new nonirritating radiopaque compound has been devised, consisting of mono-iodomethane sulphonate of sodium (skiodan) (40 per cent) with acacia (20 per cent).

4. This chemical compound does not release free iodine and is rapidly excreted from the body through the urine. The acacia, added for viscosity, does not have a foreign body effect as do poppy seed or sesame oils.

5. Adequate animal experiments were conducted to demonstrate, histologically and chemically, the correctness of the foregoing statements before beginning the clinical use of this medium with patients.

6. It has now been used in our clinic in a series of patients over a period of nearly two years without clinical evidence of inflammatory or other reactions, either immediate or delayed. Moreover, the x-ray pictures appear to be more distinct than with the iodized oil preparations.

2. *Rate of Resorption as Shown by X-ray.*—X-ray films were taken of rabbits in which one horn of the uterus had been injected with 1 c.c. of skiodan-acacia, and ligated near the cervix. Various time intervals following injection were chosen, to study the rate at which the shadow of the injected horn disappeared, and at which a shadow appeared in the bladder due to absorbed and excreted skiodan.

The shadow of the uterus, at first sharp and clear, became faint toward the end of an hour; in some cases it disappeared completely within one or two hours. In only one instance was the shadow of a Fallopian tube identified. It is probable that the rabbits' tubes, being of small caliber, do not contain enough of the radiopaque material to cast a shadow except when they are unusually well developed.

Coincidentally with the fading of the uterine shadow, sufficient skiodan is absorbed and excreted into the urine to cast an increasingly distinct shadow of the bladder. This shadow is first seen, under our experimental conditions, about thirty-five to forty minutes after the uterus has been injected.

Dr. Barlow reports that experiments on albino rats show that the incidence of positive abdominal films is 100 per cent within five minutes after injection, 80 per cent within ten minutes, 40 per cent within fifteen minutes and only 30 per cent within twenty minutes. Clinical observations confirm these findings.

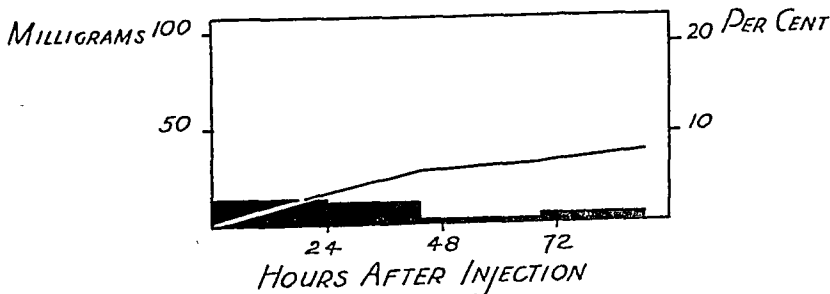


Fig. 7.—Iodized oil (600 mg.) injected directly into peritoneal cavity. Compare with Figs. 5 and 6, noting relative slowness and incompleteness of resorption and excretion. (Note: Vertical scale is twice that of Figs. 5 and 6.)

3. *Excretion of Compound in the Urine.*—Rabbits were given injections of skiodan-acacia, and their total output of urine collected at one- to three-day intervals. Iodine was determined on aliquots of these specimens using a modification of Kendall's method.

One cubic centimeter of skiodan-acacia was injected into the right uterine horn of rabbits, and the uteri ligated proximally. The excretion of the iodine compound in their urine was then studied. The greater part of the iodine compound administered was excreted at the end of the first eighteen hours, after which the rate fell off sharply. Substantially all of the injected skiodan had been accounted for by the end of the third day after injection.

Since these experiments gave no clue to the site from which the compound was absorbed, two further experiments were carried out. In the first, 1 c.c. of skiodan-acacia was injected directly into the lumen of one uterine horn of the rabbit, and ligatures tied proximally and distally to the site of the injection, the distal ligature including about one-half of the length of the tube. Animals were placed in metabolism cages, and their output of urine analyzed at intervals for iodine compound as in the previous experiment. The rate of absorption of skiodan through the intact uterus and tube is distinctly lower than from the peritoneum. For comparison, the rate of absorption of iodized oil, and the excretion of its iodine in the urine, were studied by methods similar to those used in the previous experiments. Excretion was found to occur at a markedly lower rate, but it is impossible to compare this rate with that at which skiodan was excreted, since, in rabbits receiving iodized oil, the urinary output decreased profoundly. The rate of iodine excretion increased slightly as the daily volume of urine again approached normal.

5 c.c. of this preparation into the genital tract of a rabbit, and at the same time injected the same amount of lipiodol into a rabbit of equal size, with a view of comparing the value of these media.

The films indicate that lipiodol is more radiopaque than the skiodan but that it shows less detail. The rabbit that received the skiodan apparently suffered no discomfort following its introduction, while the rabbit that received the lipiodol had definite abdominal cramps.

An autopsy a few days afterward in both rabbits showed no changes in the uterus and tubes of the rabbit that received the skiodan, while definite congestion was demonstrated in the rabbit injected with lipiodol.

Dr. Titus' presentation marks an evolution in the use of radiopaque media in gynecology, and we will give it a trial and compare it with our fifteen years of experience in the use of lipiodol and our shorter experience with thorad in the hope that it will supersede these media in diagnostic precision in the field of gynecology.

DR. JOSEPH L. BAER, CHICAGO, ILL.—At the Michael Reese Hospital we have had to date no untoward results from lipiodol. It has the advantage also of remaining in situ and allowing the genitalia to be studied. We have not had the inflammatory end results and difficulties which Dr. Titus describes, and therefore thus far have been quite content to go on with the use of lipiodol, which of course remains over long periods of time but which is apparently innocuous in the human being.

DR. TITUS (closing).—Those of us who have not had difficulty with the use of iodized oils have been extremely fortunate. I have had three very distinct and definite reactions, one a sharp one where the patient proved afterward to be sensitive to iodine. Another developed a parametritic mass, evidently an arousing of an old and unsuspected infection.

The rapid resorption and disappearance of the skiodan are distinct advantages in view of the fact that there have been a number of reports in the literature of encysted masses of oil, with evidences of localized peritonitis, found at laparotomy even a long time after treatment of this sort.

I can confirm Dr. Campbell's experimental findings, as ours were similar to his in that the x-ray shadows seemed sharper with this medium than with iodized oil.

The preparation was made up as a concentrated aqueous solution of skiodan, and then diluted down with acacia in solution so that the mixture finally contained 40 per cent of skiodan and 20 per cent of acacia, the balance being water. Acacia is added for viscosity, as explained in the paper, the mixture being approximately the same in this respect as ordinary iodized oil.

7. Further studies are now being made by us to determine the rate of excretion of mono-iodomethane sulphonate of sodium through the urine, and also the fate of acacia injected into body cavities.

It is suggested that this preparation may be of distinct use in bronchoscopic work. Our Research Laboratory is now collaborating with the Department of Neuro-surgery at this Hospital in an effort to develop a modification of this preparation suitable for intraspinal and intracranial use.

We are indebted to the Winthrop Chemical Company for a generous quantity of supplies used in these studies, and to Dr. O. W. Barlow of their Research Laboratories for his active cooperation and helpful suggestions.

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DISCUSSION

DR. ALEXANDER M. CAMPBELL, GRAND RAPIDS, MICH.—When in the field of gynecology a comparatively new diagnostic procedure is suggested, which involves the entrance of a foreign substance into the inner genitalia, which nature has guarded with certain defense barriers, the physician who assumes the responsibility of making such a test should make the following inquiries:

1. What is the danger attending such a procedure?
2. How much pain and disability will this measure cost the patient?
3. Has the test been done in a sufficient number of cases, and with such a satisfactory technic that conclusions of value may be drawn from it?
4. What information can be obtained that cannot be gained by a careful gynecologic examination, made under anesthesia if necessary?
5. Can its field of usefulness be extended toward more precise diagnosis in gynecology?

After an experience of fifteen years in which we have used lipiodol in utero-salpingography we have never observed the clinical evidences of infection or other reactions referred to by Dr. Titus, and reported by others. We have attributed this to the fact that we have used this in selected cases, in our sterility studies, in private practice, and have been extremely careful and gentle in our technic.

As our experience increased, however, we observed that for intrauterine diagnosis lipiodol has definite limitations. We have, therefore, searched for a more satisfactory medium, and were much interested in the reports of Guttman and Stahler, who in 1933 used as a medium thorium dioxide solution for uterine and tubal shadow demonstrations. They warned of its irritating qualities and after using it a few times we discontinued it for that reason. Soon after this my associates attempted to develop a more satisfactory medium and succeeded by using a colloidal suspension of thorium hydroxide. This preparation is known as thorad and is injected into the uterus by the open method. It adheres to the mucous membrane and gives satisfactory demonstration of the relief of the endometrium. We use this preparation routinely in an attempt to diagnosticate minute intrauterine lesions, such as early carcinoma, polyps, and small fibroids where no pathology can be demonstrated by the ordinary careful gynecologic examination. In the investigation of uterine bleeding it is of value. When lesions are diagnosed by this method, it is a guide to the placement of radium when radium is used in the uterus. In our experience it has been a most valuable diagnostic aid.

We have had no personal experience with skiodan in the human female genital tract. Dr. Titus sent us some ampoules of it a few weeks ago, and we injected

median incision when a moderate amount of room was required and a mediolateral when the opposite obtained. The lateral incision is best made on the side of the presenting part, in other words, a right episiotomy in a right position and a left episiotomy in a left position. Occasionally it may be advantageous to incise the two sides.

In a primary repair, emphasis must be placed on layer sutures and approximation without tension. Mass suturing often leads to a rigid, scarred, sensitive pelvic floor. Sutures which are set snugly at the time of repair will be found to be cutting through the tissues in twenty-four hours, when the edema has set in and, conversely, sutures which appear to be loose at the intervention will be set properly the next day. The puerperium is shortened rather than prolonged and involution occurs faster if the repair is done soon after delivery, but, if the parturient is not seen shortly after labor, a minimum of three months are allowed to elapse before operating. Involution has then taken place, the edema has disappeared, scar tissue has formed between the torn edges and, in my experience, better operative results are obtained than when a so-called intermediate operation is attempted about ten days after labor.

PREOPERATIVE PREPARATION

The patient is prepared by thoroughly emptying the bowel by means of castor oil, administered four days and two days before operation. She is given a cleansing enema, preferably saline, the afternoon before, but none the morning of operation, and, for the two preceding days her diet is one that contains but little residue. Under anesthesia the operative field is prepared by gently scrubbing the external genitals and the vagina with tincture of green soap and warm sterile water, using gauze at the end of a sponge stick. The parts are then irrigated with a solution of potassium mercuric iodide, 1 to 1,000, strong antiseptics not being used.

TECHNIC OF OPERATION

Two general principles are employed in the repair of a complete laceration of the perineum: (1) The flap method, advocated by Warren, (a), and modified by Ristine, (b), Farrar, (c), Miller, (d), and others. (2) The layer method of repair with or without rectal suture. I have employed the latter method with rectal suture and since my results have been satisfactory, I have not had occasion to change.

The pelvic floor is opened by a capital H-shaped incision. The lateral incision on each side extends from a point below the duct of the vulvovaginal gland to the retracted end of the sphincter. The transverse incision joins the two lateral by running through the edge of the scar tissue uniting the rectal and vaginal walls. A flap of posterior vaginal wall is raised upward exposing the rectum which is separated from the levator ani muscles by blunt dissection. The anterior rectal wall is picked up by an Allis forceps at the upper angle of the tear and put on stretch, the scar tissue is trimmed from the edges and the torn edges are united by interrupted sutures of fine prepared silk (Dermal), the knots being tied within the bowel lumen. The perirectal tissues are approximated over the first suture line by a continuous stitch of No. 0 or No. 00 chromic catgut, avoiding constriction of the tissues. The perirectal tissues are further approximated, without tension, by figure-of-eight sutures of the same material. The rectal wound is thus closed in three layers. The torn ends of the sphincter ani muscle are dissected out of their bed of scar tissue and approximated with a figure-of-eight suture of No. 1 chromic catgut. If there is tension on the sphincter ends a reinforcing suture of silkworm gut may be introduced by passing

COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA*

MANAGEMENT AND END RESULTS

LOUIS E. PHANEUF, M.D., Sc.D., F.A.C.S., BOSTON, MASS.

LACERATION of the perineum involving the anal sphincter and rectovaginal septum has always been looked upon as one of the most discouraging conditions affecting woman. In a previous publication, I¹ reported the end results of 42 cases. Since then, during a period of nearly ten years, I have operated upon 50 more patients, a total of 92 operations in a period of approximately twenty-two years, or about 4 a year. Improvement in obstetric practice has been responsible for a diminution of this disorder during the last decade. Several of my patients had carried the affliction for a number of years, one of them 27, and another 50 years. A great many had occurred before episiotomy was resorted to as frequently as it is today. Ten of the women in the series had had an unsuccessful primary repair and presented themselves with complete separation of the sphincter ends, a large rectovaginal fistula and a bridge of perineal tissue which had held between the two. A rectovaginal fistula may occur during the process of healing by the infection of some of the stitches. Most of the small ones heal spontaneously after the catgut knot is absorbed or discharged, while others need a subsequent closure. In 9 patients I sutured the tear shortly after childbirth and in 83 the repair was accomplished as a gynecologic operation. These 92 patients were obtained from a wide geographic area and represented an occasional complete laceration in a given district. A third degree tear of the perineum, with its not infrequent accompanying rectovaginal fistula, may be avoided in practically all instances by resorting to an episiotomy. The manual dilatation of the perineum advocated by some obstetricians may decrease the incidence of this disorder but does not give the protection obtained by a properly performed incision. Furthermore, with manual dilatation the separation of the levator ani muscles under the intact mucous membrane and skin may occur with a resultant rectocele, a condition but seldom encountered after well-sutured perineal incisions. An episiotomy may be median or medio-lateral. The protagonists of the mediolateral object to the median incision or perineotomy on the principle that if the median incision is extended by the advancing presenting part it may go through the sphincter ani muscle. This complication may be prevented by continuing the incision so that it encircles the anus on one side, thus avoiding injury to the sphincter. It has been my custom to use a

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, North Carolina, May 30, to June 1, 1938.

Table I summarizes the 92 cases reported in this paper. In this series one patient had been unsuccessfully operated upon twice, and seven patients once. The youngest patient was 7 years of age and the oldest 70 years. The average age was 36 years. Spinal anesthesia with a small dose of novocaine crystals was resorted to 15 times and general anesthesia 77 times.

TABLE III. ADDITIONAL LESIONS IN THE GROUP OF 83 PATIENTS WITH OLD COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA

Laceration of right labium majus	1
Prolapse of rectum	3
Rectal polyp	1
External thrombotic hemorrhoid	1
Rectocele	4
Cystocele	13
Vesicovaginal fistula	1
Laceration of cervix	31
Erosion of cervix	4
Cervical polyp	2
Hypertrophied cervix	2
Myoma uteri	1
Procidentia uteri	3
Second degree prolapse	3
Descensus uteri	1
Third degree retroversion	1
Second degree retroversion	2

TABLE IV. ADDITIONAL OPERATIONS IN THE GROUP OF 83 PATIENTS WITH OLD COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA

Repair of right labium minus	1
Moschcowitz operation for prolapse of rectum	1
Fundic hysterectomy, bilateral salpingo-oophorectomy	
Bladder advancement, fixation of uterus to abdominal wall	1
Excision of rectal polyp	
Evacuation of clot from external thrombotic hemorrhoid	1
Kelly operation for relaxed vesical sphincter	1
Resection of suburethral fold	1
Operation for cystocele	10
Dilatation and curettage	31
Cauterization of cervix	2
Conization of cervix	1
Cervical polypectomy	2
Right trachelorrhaphy	2
Bilateral trachelorrhaphy	20
Schröder amputation of cervix	2
Amputation of cervix	9
Interposition operation	5
Vaginal hysterectomy	2
Round ligament suspension of the uterus	2

NOTE.—The laparotomies for suspension of the uterus were done two weeks after the plastic repair, while the Moschcowitz operation for prolapse of the rectum and fundic hysterectomy were performed two weeks before the reconstruction of the complete tear of the perineum.

Ninety-four additional operations were performed on this group of 83 patients with complete laceration of the perineum and rectovaginal fistula, as depicted in Table IV. Two laparotomies were performed. In one patient the uterus was suspended two weeks after the plastic repair, while in another the Moschcowitz operation for prolapse of the rectum and a fundic hysterectomy were resorted to two weeks before the reconstruction of the complete tear of the perineum. For obvious reasons an abdominal operation should not be performed in conjunction with the reconstruction of a perineum lacerated in the third degree.

it through the skin of one side, the sphincter muscle and the skin of the other side, to be tied at the completion of the operation. The excess of vaginal flap is resected, the edges of the vaginal incision are united with No. 1 chromic catgut interruptedly, and the levator ani muscles and their fascia are brought together by three interrupted stitches of the same catgut. The external perineum may be closed in three ways: (1) By approximating the triangular ligament with a running stitch of No. 0 or 00 tanned catgut, and the skin by a subcuticular or continuous suture of the same material; (2) by interrupted sutures of No. 0 chromic catgut, which in their course pick up the united levator ani muscles to obliterate dead space; (3) if there have been previous attempts at repair and if considerable scar tissue is present, interrupted fine silkworm gut sutures may be used to advantage in the closure. Emphasis must be placed on fine suture material and approximation without tension. As my experience with this operation has increased, I have used finer and finer catgut.*

POSTOPERATIVE CARE

Morphine sulphate and deodorized tincture of opium are administered as necessary. For the first six days the diet consists of hot and cold fluids, without residue such as beef tea, strained soup, bouillon, the white of an egg, with two ounces of strained orange juice and water to make four ounces, tea with lemon and black coffee. Milk is not allowed. The external suture line is painted with a 4 per cent solution of mercurchrome after micturition or catheterization. After forty-eight hours a short 4 per cent boric acid douche is given daily, using a soft rubber catheter as a tip. On the morning of the seventh day the patient is given a Seidlitz powder. One-half hour later six ounces of warm sweet oil are instilled into the rectum and retained. She is given a low soapsuds or saline enema when the desire to empty the bowel becomes apparent and she is instructed not to strain. After this a soft diet is allowed and by the ninth day a full diet. The silkworm gut suture or sutures, if used, are removed on the ninth day, she is allowed out of bed on the twelfth day and usually discharged on the fourteenth or fifteenth postoperative day, to be examined again one month later.

TABLE I. COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA

Summary of Cases

Fresh complete laceration of the perineum	9
Old complete laceration of the perineum	33
Complete laceration of the perineum with involvement of anterior rectal wall	34
Complete laceration of the perineum with involvement of anterior and posterior rectal walls	1
Complete laceration of the perineum with rectovaginal fistula	10
Rectovaginal fistula	5
Total	92

TABLE II. COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA

Etiology

1 Complete laceration, child 7 years of age, impaled on an iron picket fence.
1 Complete laceration, child 7 years of age, following rape.
1 Rectovaginal fistula following a perineotomy for vaginismus.
1 Rectovaginal fistula following an operation for fistula in ano.
88 Complete laceration and rectovaginal fistula resulting from the trauma of labor.

*For the illustrated technic of this operation the reader is referred to the AM. J. OBST. & GYNEC. 17: 475, 1929.

and scar tissue is allowed to form, it becomes increasingly difficult to secure a satisfactory repair. If a successful repair is not attained there is imperfect development of the lower rectum, anus, and external genitals. In this particular case it was necessary to obtain needles small enough to work with from the eye department of the hospital. Healing took place by first intention and she secured a satisfactory anus, perineum, and vagina. She was seen for some time after operation, then disappeared. Eleven years later, when she was eighteen years old, she reported to the clinic complaining of dysmenorrhea. Examination then showed perfectly developed external genitals and anus. The scar in the external perineum could not be identified. Eighty-eight of these cases followed the trauma of childbirth, the usual etiologic factor. Complete laceration of the perineum and rectovaginal fistula is frequently complicated by other lesions. Table III shows that in the 83 patients who had old lacerations and fistulas there were 74 additional lesions.

SUMMARY

1. A complete laceration of the perineum may be prevented by employing one of three methods when the indication arises: (1) perineotomy, (2) episiotomy, (3) manual dilatation of the perineum and vagina.

2. Perineotomy, or median perineal incision, is of value when the disproportion between the presenting part and the vaginal outlet is moderate.

3. Episiotomy or lateral perineal incision should be resorted to when a great deal of room is required, as in difficult forceps operations, and when the presenting part is overlarge.

4. Manual dilatation of the perineum and vagina is a satisfactory method of preparing the birth canal before version and extraction operations.

5. The technic of operation for repair of complete laceration of the perineum and rectovaginal fistula is discussed.

6. The preoperative and postoperative care are described.

7. Emphasis is placed on careful approximation of the tissues with fine suture material applied without tension.

8. Ninety-two personal cases are reported.

9. The end result was satisfactory in 90 patients, 98 per cent, 12 of whom, 13 per cent, developed postoperative complications. In two patients, approximately 2 per cent, discharged from the hospital with small rectovaginal fistulas, the final result was not ascertained.

10. A careful preoperative preparation, meticulous technic, and postoperative care, preferably under the immediate supervision of the operator, play an important role in securing satisfactory healing.

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DISCUSSION

DR. GEORGE GRAY WARD, NEW YORK, N. Y.—Dr. Phaneuf's tenth conclusion is, I think, the crux of the whole matter. The outstanding essential for success is minute attention to detail.

Table II summarizes the etiology of the 92 cases.

The case of the first child, 7 years of age, who had a complete laceration of the perineum with involvement of the rectovaginal septum as a result of having been impaled on an iron picket fence is interesting from two standpoints. If in a child of that age, reconstruction of the parts is not carried out soon after the accident,

TABLE V. COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA
Postoperative Complications

Rectovaginal fistula	5
Ischiorectal abscess with rectovaginal fistula	2
Ischiorectal abscess with perineal sinus	1
Perineal sinus	1
Slight separation of sphincter ends	1
Small area of skin slough above sphincter ani	1
Hypertrophied tabs of rectal mucosa	1

Twelve patients had postoperative complications

They were treated as follows:

- Case 1. Small rectovaginal fistula, repaired ten months later, satisfactory end result.
 Case 2. Small rectovaginal fistula, repaired five months later, satisfactory end result.
 Case 3. Small area of skin slough above sphincter ani, satisfactory healing by second intention.
 Case 4. Small rectovaginal fistula, repaired seven months later, satisfactory end result.
 Case 5. Ischiorectal abscess with perineal sinus, right. Incision and drainage four months after original operation, healing satisfactory.
 Case 6. Slight separation of the sphincter ends, healing by scar tissue, good bowel control.
 Case 7. Small high rectovaginal fistula. This patient had been operated on for a large rectovaginal fistula which had followed a perineotomy for vaginismus. She was lost sight of.
 Case 8. Seventy years of age. Convalescence complicated by bronchopneumonia and coronary disease. Discharged from the hospital with a small rectovaginal fistula. She has refused to report for examination.
 Case 9. Perineal sinus, healed by second intention; satisfactory end result.
 Case 10. Ischiorectal abscess with fistula two months after operation. Excision of fistula, healing by second intention; satisfactory end result.
 Case 11. Hypertrophied tabs of rectal mucosa developing after operation. Injection of tabs with sclerosing solution; satisfactory result.
 Case 12. Small ischiorectal abscess and fistula, left, seven months after operation. Spontaneous drainage, healing by second intention; satisfactory end result.

TABLE VI. COMPLETE LACERATION OF THE PERINEUM AND RECTOVAGINAL FISTULA
End Results

80 patients, 87 per cent, had satisfactory results, that is, a good perineal body and sphincter control.

12 patients, 13 per cent, developed postoperative complications as follows:

6 patients had additional operative procedures and secured a satisfactory end result.

4 patients had mild infectious complications which healed spontaneously. All obtained satisfactory bowel control.

1 patient had a small rectovaginal fistula and was lost sight of.

1 patient had a small rectovaginal fistula and has refused to report for examination.

The final result in 90 of 92 patients, approximately 98 per cent (97.8 exact), was satisfactory.

The final result was doubtful in 2 patients with small rectovaginal fistulas when discharged from the hospital (approximately 2 per cent), as no follow-up could be obtained.

TABLE V. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE. OBSTETRIC SERVICE (1923-1938)

Total deliveries		9,741
Total episiotomies performed		4,874
Episiotomy, median	4,580	
Mesiolateral	281	
Lateral	13	
Total number of complete lacerations		124 (1.27%)
Total number of repair operations	129	
Results: Satisfactory	96.0%	
Partially satisfactory (patient satisfied)	2.4%	
Failures	1.6%	
Lacerations, extension of episiotomy wound		124
Sphincter tears only	54	
Rectal tears	67	
Unspecified	3	

was a failure by the layer technic, again by the Warren method, and at the third attempt by rectal sutures was successful; one patient had a partial success after a second operation, and one a failure with no further attempt.

Where the layer method with rectal sutures was used there were three failures. One patient had eight attempts with a complete failure. She had been operated upon in several hospitals and finally came to us and was repeatedly operated upon by members of our staff; altogether she had two layer operations, two Warren, again two layer, one rectal suture, and one invagination of the rectum with mattress sutures which were all failures. There was practically no sphincter muscle left and the wound was in such a distressing condition that the patient seriously threatened suicide, having already made an attempt, so I did a Sistrunk colostomy operation and she is perfectly happy today, entirely relieved of her distress.

I agree with Dr. Phaneuf's emphasis on the importance of using fine sutures rather than heavy ones. Personally I prefer a silver wire suture to reinforce the sphincter muscle and use the Warren technic by preference.

DR. LILIAN K. P. FARRAR, NEW YORK, N. Y.—I was led some years ago to try to develop a technic because of unsatisfactory results that I had had in repair of third-degree lacerations. I visited various New York clinics to see how my neighbors handled the problem. I remember one surgeon putting numerous stitches in the rectum. I thought then I probably had not sutured the rectum sufficiently but as the count rose, 20, 30, 40, 50, and 54 stitches in the rectum, I decided that technic was not for me.

I then became interested in the "Warren Apron," described by J. Collins Warren, a Fellow of this Society and Professor of Anatomy and Surgery in Harvard Medical School. I decided to try it in lacerations of the sphincter and with a laceration extending high up the rectum. Although I have not had the number of cases to repair that Dr. Phaneuf reports, I have never had a failure.

Twice I have had to put in extra sutures, the first time because the patient jumped as I removed a wire and once when an intern placed the legs of the patient in stirrups and the sutures on one side cut out. Both cases, however, healed perfectly. I keep a finger in the rectum while placing catgut and wire sutures and then after a change of gloves I tie the sutures.

I do not believe wire sutures are absolutely necessary. Best of Nebraska and Miller and Brown of Ann Arbor report good results by this technic and they use catgut only. Wire sutures are, however, the tradition of the Woman's Hospital, and as I have had satisfactory results with them I continue to use them. (For a full description and illustrations of the operation, see *Surgery, Gynecology and Obstetrics*, April, 1930, p. 741, and also Curtis, A. H.: *Obstetrics and Gynecology*, Vol. III, Philadelphia, 1933, W. B. Saunders Company, pp. 77-83.)

DR. FREDERICK C. HOLDEN, NEW YORK, N. Y.—A number of years ago Dr. Ralph Pomeroy called my attention to the fact that if a sphincter ani was thor-

Either technic of operation, the flap or the layer method, may be successful. The type selected should be adapted to each case, although personally I prefer the flap method wherever possible.

In the postoperative treatment of these cases two methods are employed by different operators: Delayed bowel movements where the bowels are kept inactive for a period of seven days or longer, and the method of giving saline cathartics in small repeated doses early to produce liquid stools after the third or fourth day. Both of these methods may be successful, and I am inclined of late to the earlier movement of the bowels rather than tying them up for a long period.

I have had the records at the Woman's Hospital gone over for the past fifteen and twenty years and find the following data and end results:

TABLE I. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE. TOTAL NUMBER OF PATIENTS OPERATED UPON (GYNECOLOGIC AND OBSTETRIC)—282

Gynecologic patients	128 (20 yr.)
Number of operators	22
Cases with previous attempts at repair prior to admission to woman's hospital	20
Obstetric patients	124 (15 yr.)
Total patients with satisfactory result	242 (96.02%)

TABLE II. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE (1918-1938). GYNECOLOGIC SERVICE

Total number of patients operated upon	128
Total number of operations performed	152
Patients having more than one operation	12
Total patients with satisfactory result (all techniques)	122 (95.31%)

TABLE III. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE. GYNECOLOGIC SERVICE. POSTOPERATIVE TREATMENT

	EARLY	LATE
Warren technique	18	15
Layer method	45	11
Layer method with rectal sutures	32	7
Total	95	33

TABLE IV. OPERATION FOR LACERATION OF PELVIC FLOOR, COMPLETE. GYNECOLOGIC SERVICE. TECHNIQUE USED ON PRIMARY ATTEMPT AT REPAIR

	TOTAL	SUCCESS	PARTIAL SUCCESS (PATIENT SATISFIED)	FAILURE
Warren technique	33	30	1 (93.93%)	2
Layer method	56	45	4 (87.5 %)	7
Layer method with rectal sutures	39	34	2 (92.3 %)	3

In the gynecologic service where the Warren or flap technic was used, one patient died of pulmonary embolus; three patients required resuture operations, all successful; one patient otherwise successful, developed a fistula. There were two failures, one having an infection of the wound and hemorrhage, and one a failure of union of sphincter fibers.

Where the layer method was employed, two patients required resuture operations, both successful; one patient had a fecal impaction on the twenty-third postoperative day with rupture of the sphincter, but was ultimately a success after healing by secondary intention; two cases were successful after a second attempt with rectal sutures; one a success after a second attempt by the layer method. One case

Correspondence

The Dosage of the Estrogens

To the Editor:

In the editorial on "The Dosage of the Estrogens" which appeared in the September issue of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, a passage in the first paragraph (last line) as well as in the third paragraph gives the impression that the terms "estradiol" and "theelol" refer to the same substance. The care with which these editorials are read is attested by the fact that we promptly received a number of inquiries as to whether it was really true that theelol was the same as estradiol.

I would greatly appreciate it if you would publish a statement making it clear that these two substances are distinct.

(Signed) MAX GILBERT, M.D.,
Medical Research Division, Schering Corporation.

The above letter brought the following reply from Dr. Robert T. Frank, the writer of the editorial referred to:

To the Editor:

Our attention has been called to an unclearness in the nomenclature of estrogens mentioned in the editorial in our September issue.

"Estradiol" corresponds to the terminology of dihydrotheelin and not of theelol which, according to the same terminology, corresponds to estriol.

(Signed) ROBERT T. FRANK, M.D.

To the Editor:

We would like to ask for your help in the matter of procuring fresh tissue specimens of hydatidiform mole and chorionepithelioma. In this laboratory we have been studying living cells of the early placenta in tissue culture and, therefore, have been anxious to compare malignant with nonmalignant cells derived from trophoblast. We are also very much interested in the production of prolactin by the cells of the placenta when they are maintained for long periods of time in continuous culture. One of the great difficulties in pursuing work of this sort with human material lies in the fact that it is difficult to get fresh specimens at fairly frequent intervals.

We would greatly appreciate any efforts on your part in helping us to get specimens of hydatidiform mole and chorionepithelioma. It is important that the specimens be collected under aseptic conditions and that they be placed in a sterile tightly stoppered bottle without the addition of any solution such as salt, and shipped to us by air mail, special delivery, and that we be notified by telegram "collect" that the specimen is being sent. A note on some of our work appeared in *Science* recently (*Science*, September 30, 1938).

GEORGE O. GEY, M.D.

The Johns Hopkins Hospital,
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oughly and carefully dilated just before delivery, there was much less likelihood of subsequent injury to the sphincter by an extension of a perineal laceration or of a median episiotomy.

Where an operative procedure is indicated, I prefer the Warren operation which I do without the silver wire sutures.

DR. G. D. ROYSTON, St. Louis, Mo.—There are two things we have found of special value: first, that the intestine should be kept empty after operation until there has been time for satisfactory repair; and second, that defecation should be produced without trauma, from enemas and from unnecessary efforts at cleansing the repair.

Some years ago, I reported from the Washington University Clinic some 68 repairs of complete perineal laceration on 62 different patients. These 68 operations were performed by 13 or 14 men, including house surgeons and junior assistants. This comparative study showed that the best results were obtained in patients who were given liquid diet, without milk for two days prior to operation, and evacuated with castor oil and enemas on each of these two days.

Fine catgut, preferably No. 1 or smaller, in continuous suture gave better results than interrupted sutures, coarser catgut, or nonabsorbable material. The repaired wound was left strictly untouched by pitcher douches or other cleansing efforts along the line of repair. After operation, opiates were freely given. The postoperative diet consisted of liquids without milk or fruit juices until signs or symptoms of autointoxication appeared, when mineral oil, 1 ounce three times daily, was given for two days, followed by a bottle of citrate of magnesia, which usually produced a soft stool.

This method gave on hospital discharge only 4 failures to obtain primary union among 31 cases, as compared with 8 failures among 26 given enemas and 4 failures among 10 with spontaneous defecation. The result was unknown in one. The first defecation varied from one to twenty-three days after operation, most patients being carried from eleven to fifteen days without defecation following the repair. Both methods of operation were used, though we prefer the flap method.

DR. JOSEPH L. BAER, CHICAGO, ILL.—There has been no distinction made in the discussion nor in the original paper of the essential difference between the repair of a fresh obstetric injury and an old gynecologic third degree tear. In our experience we have no recollection nor record of a fresh repair failing to heal. It is with the old repairs that occasional difficulty arises.

Dr. Norman Miller reported a procedure used routinely in order to place the anteriorly united repair at rest. It is a subcutaneous posterior division of the sphincter, at the end of an operation being done to unite an old anterior separation. He has been most pleased with this procedure and finds that the posterior incision reunites spontaneously. I have done this several times, though with the fear that I might produce a posterior hematoma in the field, but healing was uneventful.

DR. PHANEUF (closing).—Dr. Farrar's technic of the flap method differs entirely from the one which we have used, but she has shown that equally good results could be obtained by it.

Dr. Holden's recommendation of the dilatation of the sphincter before performing an incision in the perineum at the time of delivery is logical and should be extremely helpful as a prophylactic measure in the prevention of complete tears.

I do not see the necessity of tying up the bowels for as long a period of time as Dr. Royston has advised.

(The remaining papers read at the meeting of the American Gynecological Society will appear in the December issue, namely, those of Caldwell, Schwarz, Bartholomew, and Montgomery.)

Evidence that toxemia of pregnancy is the result of absorption of poisonous protein split products of autolysis of infarcted placental tissue, was further supported by producing the clinical symptoms of eclampsia and characteristic pathologic changes in liver and kidneys of guinea pigs by repeated injections of autolysate of human placental tissue.

In January, 1934³ we advanced the theory that autolysate of placental tissue probably contains a higher content of guanidine than that of any other tissue, because of the fact that placental tissue contains twice as much arginine as any other tissue.⁴ A possible mode of derivation of guanidine from arginine was described, and since guanidine is known to raise blood pressure and produce convulsions,⁵ the peculiar eclamptogenic property of autolyzed placental tissue may thus be explained. This theory is supported by the fact that Kracke, in giving repeated injections of autolysate of other tissues to produce artificial leucocytosis in rabbits, has never produced convulsions, although they may be readily produced by autolysate of placenta tissue.⁶

In April, 1936⁷ we described certain focal changes visible beneath the endothelium and in the wall of some of the smaller placental arteries and apparently more frequent in toxic cases, which were typical, in appearance, of cholesterol vascular change, such as is found in coronary thrombosis and in experimentally produced atherosclerosis in cholesterol fed rabbits.⁸ Large fat cells appear beneath the endothelium, narrowing and distorting the lumen and invading and weakening the vessel wall.

It therefore seemed probable that the well-known hypercholesteremia of pregnancy supplied the missing link in the chain of evidence by which the infarction is readily explained, through its tendency to narrow the vessel lumen, roughen the endothelial lining or weaken the vessel wall, thereby causing occlusion, thrombosis or rupture. We still adhere to the importance of the role played by the trauma of fetal movements, for it has been shown⁹ that cholesterol vascular change occurs much more readily at the site of trauma to the vessel wall, and, following such change, trauma, in turn, is much more likely to cause rupture of the vessel at that point.

In the same publication, we furthermore stressed the importance of the role which the pituitary gland probably plays through control of cholesterol metabolism, and which hypothyroidism undoubtedly plays in causing excess hypercholesteremia and that thyroid extract or iodine, when indicated, may control excessive hypercholesteremia.

In pregnant women of this particular endocrine type, hypercholesteremia renders them potential victims of toxemia. In other words, certain patients who seem prone to develop toxemia in successive pregnancies, are not increasingly susceptible to toxemia because of the first attack, but because of their fundamental endocrine type and hypercholesteremia.

In addition, we stressed the fact that a cholesterol-rich or -poor diet influences the degree of hypercholesteremia and is, therefore, an important determining factor in the frequency of eclampsia. This probably ac-

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Original Communications

DIAGNOSIS OF THE OCCURRENCE OF TOXEMIA OF PREGNANCY BY EXAMINATION OF THE UNKNOWN PLACENTA*

STUDY OF 100 CASES

R. A. BARTHOLOMEW, M.D., AND E. D. COLVIN, M.D., ATLANTA, GA.

(From the Department of Obstetrics, Emory University School of Medicine)

IN DECEMBER, 1932¹ we described the lesions found on section of 1,000 consecutive placentas from both normal and toxic cases, and in the classification proposed at that time, recognized the acute type of placental infarct first described by Young,² and noted the consistency with which it was found in cases of toxemia of pregnancy.

Contrary to Young's hypothesis, which attributed the infarct to blockage of the maternal blood supply, our investigations indicated it resulted from blockage of the fetal blood supply, due, probably, to thrombosis or even rupture, induced by the trauma of vigorous fetal movements on the exposed fetal arteries on the surface of the placenta. Positive proof that actual rupture of these vessels may at times occur, is seen in Figs. 5 and 8 of the above-mentioned article.¹ Furthermore, thrombosis of the villous capillaries is frequently found in infarcts of the more acute type.

In no other situation or under no other condition, do we find a circulation so unprotected and at the same time so exposed to trauma as is the fetal circulation on the surface of the placenta. Furthermore, the shape and size of the uterus, the relatively greater freedom of motion of the fetus and the relation of the placental site to the extremities of the fetus, render the human placenta more subject to trauma than that of many of the lower animals.

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

feature which might enable one to remember the specimen several weeks after delivery. The size of the placenta did not furnish a clue as to the identity of any case, since there was a number of slightly premature labors including both normal and toxic cases.

As an aid in recognition and classification of the lesions commonly found in the placenta and to create a better understanding of the criteria by which the degree and type of toxemia are judged, color photographs and descriptions of the lesions have been included.

The lesions have been designated by the letters *A*, *B*, *C*, *D*, *E*, *F*, *G*, and *H*. For emphasis and convenience, the italicized letters indicate the infarcts which are associated with increasing degrees of toxemia.

Infarct *A* (Fig. 1) is recognized grossly by its white color and firm consistency. The etiologic factor is apparently a gradual sclerosis which first affects the small terminal placental arteries on or near the margin of the placenta. The dependent villi undergo slow degeneration, extending over a period of one to several months. Since the surface of the villi serves as an endothelium to the intervillous blood channels, the slow necrosis induces thrombosis of the maternal blood, which gradually becomes hyalinized, causing the infarct to become firm and white from absence of circulation. Microscopically, the pale, faintly stained "ghost villi" appear to be imbedded in the homogeneous pink-staining hyaline substance (nonvascular or solid portion of Infarct *B*, Fig. 2).

There can be no toxemia resulting from Infarct *A*, not only because the protein split products of villous necrosis and autolysis are formed too slowly but also because intervillous thrombosis and hyalinization prevent diffusion of these products into the maternal circulation.

Infarct *B* (Fig. 3) is recognized by its yellow color and firm consistency. It is likewise usually found on or near the margin of the placenta. The etiologic factor is apparently a sclerosis or obliterative endarteritis slightly more active than in Infarct *A*. The thrombosed intervillous blood channels are incompletely hyalinized and the degenerating red cells have not completely disappeared, thereby imparting a yellow color to the lesion (vascular or open areas of Fig. 2).

In the early stage of formation, Infarct *B* may have been responsible for a transient slight edema or albuminuria or a slight rise in diastolic blood pressure, but it soon becomes incapable of causing toxemia for the reasons mentioned under Infarct *A*.

Infarct *C* (Fig. 4) is recognized by its brown-yellow color and moderately firm consistency. It is likewise usually found on or near the margin of the placenta but may occur elsewhere. The etiologic factor is probably a progressive arterial occlusion at the site of cholesterol vascular change, and more rapid than in Infarct *B*. Hyalinization of the thrombosed intervillous blood is incomplete, and there is active intervillous circulation in some parts of the infarct. The brown-yellow color of the lesion is due to partial degeneration of the red cells enmeshed in strands of fibrin. Pyknosis and karyorrhexis may be seen (Fig. 5).

Since necrosis of the villi has been slightly more rapid than in Infarct *B*, it is probable that peptone, one of the early products of autolysis, is present in sufficient amount to inhibit complete thrombosis, thereby permitting diffusion of small amounts of guanidine and histamine into the maternal circulation with manifestations of toxemia.

Infarct *C* may therefore be responsible for moderate edema, albuminuria, and hypertension in the latter part of pregnancy which may persist for some time without increase or may subside as thrombosis and hyalinization extend.

Clinically, we are wont to credit improvement in the patient to our therapeutics, but the real agent in bettering the patient's condition is increasing intervillous thrombosis which closes the paths of diffusion of the toxic protein split products of placental autolysis.

counts for the geographic variations in the incidence of eclampsia, and the lessened frequency of eclampsia in Germany during the World War.

The above-mentioned fundamental factors of hypercholesteremia, hypothyroidism, cholesterol vascular change in the placental arteries and placental infarction have since been emphasized by Patterson, Hunt and Nicodemus¹⁰ in 1938, but comment on certain features of their theory is deferred to the concluding portion of this article.

Our previous knowledge and classification of placental lesions were developed by examining "known placentas"—that is, the clinical record of the patient was reviewed just before the placenta was cut. One is likely to be influenced in his judgment of a questionable lesion, if he knows, in advance, whether or not the patient had toxemia. It is one thing to examine the cut strips of a "known placenta" and find lesions which may be regarded as significant. It is quite another thing to examine the cut strips of an "unknown placenta" and commit oneself to a statement as to whether the patient had toxemia, and if so, whether it was mild, moderate, pre-eclamptic, eclamptic, or abruptio in type. This is the acid test for the specificity of certain placental infarcts for toxemia.

The fact that the relationship of acute placental infarcts to toxemia has not been generally appreciated or accepted, is due to neglecting to prepare and fix the placenta properly before cutting it, and to overlooking the more acute types of placental infarcts. The placenta should be prepared by cutting away the membrane, stripping the amnion from the fetal surface, wiping the maternal surface free of blood and fixing it for three to four weeks in 10 per cent formalin solution. It should then be examined by cutting it in strips of 0.5 to 1 cm. in diameter.

The investigation herewith described is based upon the examination of 100 placentas obtained from cases of normal pregnancy, mild toxemia, pre-eclampsia, eclampsia and abruptio and a few cases of pre-existing vascular disease associated with hypertension. Seventy-six placentas were obtained from our private patients, the remainder from the Colored Division of Grady Hospital and from other physicians.

The placentas, prepared in the above described manner, were examined as "unknowns," one of us (E. D. C.) removing the label immediately preceding the examination, following which the other (R. A. B.), dictated a description of the lesions found and an opinion as to whether the patient showed hypertension or albuminuria during pregnancy, and if so, as to the severity and type of toxemia. The clinical record was later examined and the pathologic and clinical diagnoses were compared. Through this method of examination, we have been able to arrive at a much more accurate classification of placental lesions than any we have heretofore proposed, and have found it possible to diagnose the occurrence of toxemia from the appearance of the placenta in 80 to 90 per cent.

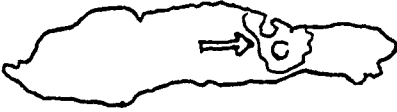
With the exception of one placenta which showed extensive firm white infarction involving about one-fourth of the maternal surface, and several specimens of abruptio placentae, showing indented compressed placental tissue, there was no placenta which had any distinguishing



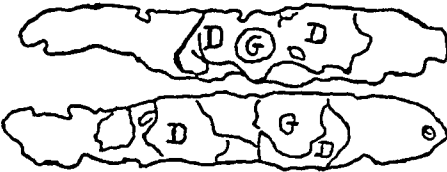
1. Onset of mild toxemia at 35th week (Infarct B)
Acute exacerbation at 39th week (late E Infarct).



3. Onset of very mild toxemia at 35th week (Infarct B). No exacerbation.



4. Toxemia, increasing from mild to moderately severe, over a period of three to four weeks, blood pressure increasing to 160/100 (Infarct C). Labor induced at 33rd week.



6. Acute toxemia of two weeks' duration (late D Infarct), terminating in eclampsia.



7. Onset of acute toxemia at seven months (late D Infarct), terminating in abruptio two weeks later. Very severe hematuria.



9. Mild toxemia 35th to 38th week (Infarct B); acute pre-eclampsia 39th week; induction of labor; three post-partum convulsions.



10. Moderately severe toxemia 37th week (early D Infarct), abruptio 39th week, labor induced. Survival of child favored by site of infarct and separation on margin.

2.

Photomicrograph showing pale avascular areas with "ghost villi" and hyalinized intervillous blood characteristic of nontoxic type "A" infarct, and slightly vascular areas with slow necrosis, characteristic of slightly toxic type "B" infarct.

5.

Photomicrograph showing type "C" infarct. Necrotic villi with open intervillous circulation predominate, but there are many areas of types "A" and "B" infarction also present. Case of moderately severe toxemia.

8.

Photomicrograph showing type "D" infarct. Necrotic villi with open intervillous circulation. Many villi disintegrating. No areas of types "A," "B," or "C." Case of eclampsia.

Infarct *D* is *acute* and may be found in an *early* or a *late* stage. The *late* stage (Figs. 6 and 7) is easily recognized by its distinct brown color. The consistency is so much firmer than the surrounding normal tissue that, on bending the strip, the lesion holds together or finally cracks rather than bends.

It may be visible on the maternal surface or concealed within the substance. The etiologic factor is apparently occlusion or thrombosis at the site of cholesterol change in a small placental artery. The exciting factor is probably the trauma of fetal movements which breaks the endothelium over the accumulated fat cells. Necrosis of the dependent villi is much more rapid than in Infarct *C*. The villi stain poorly, show more degeneration and some disintegration (Fig. 8).

Due to greater concentration of peptone, thrombosis is inhibited, and histamine and guanidine find more ready access to the maternal circulation, producing greater evidence of acute toxemia. The infarct is brown because degeneration of the red cells is less advanced; it is not as firm as Infarcts *A*, *B* and *C* because of the lesser degree of thrombosis and the absence of hyalinization. There is sufficient meshwork of fibrin and fusion of necrotic villi in parts of the lesion to cause the area to appear more homogeneous and compact.

Some of the villi show marked distention and rupture of the terminal capillaries, which probably accounts for the small, firm clots which are often seen adjacent to or within the infarct. It is probable that the presence or absence of clot depends not only on the concentration of peptone but also on the compatibility of the maternal and fetal blood.

Since the increasing toxemia causes spontaneous onset of labor or requires induction of labor, one can only surmise what appearance the infarct would have in the final stage of degeneration.

The finding of this type of infarct indicates the patient had a moderate to severe degree of toxemia which terminated in eclampsia or required induction of labor following several weeks of increasing blood pressure and albuminuria. The size and number of the infarcts bear a definite relation to the severity of the toxemia.

The *early* stage of Infarct *D* (Figs. 9 and 10) in contrast to the *late* stage, may be easily overlooked unless one examines the placental strips with care. Due to less degeneration of the red cells, the color is only slightly brown. The area of infarction is well demarcated if the strip is held level with the eye and toward the light. The surface is more homogeneous than the surrounding tissue and is shiny. The lesion cracks rather than bends. There may be dark or slightly brown firm blood clot within or adjacent to the area.

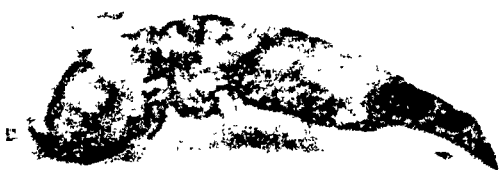
These physical characteristics are in accord with the microscopic pathology, which shows degenerated and disintegrating villi, open intervillous circulation, with occasional areas of blood clot and fibrin.

Infarct *E* is more acute than Infarct *D* and is likewise seen in an *early* and *late* stage in any part of the placenta. The etiologic factor is the same as described for Infarct *D*. The *late* stage (Figs. 11 and 12) is even more easily overlooked than the *early D* infarct. It is recognized by its dark, almost black color, and slightly firmer consistency which causes the surface to appear shiny and reflect light. On bending the strip the area cracks rather than bends. The black color is apparently due to stagnated venous blood in the congested villi, the capillaries of which are distended or ruptured. The nuclei of the villous cells are pyknotic and the stroma has a dull lusterless appearance. Soft to moderately firm dark clots may be seen within or adjacent to the area. Karyorrhexis and karyolysis may be seen in some parts of the infarct (Fig. 13).

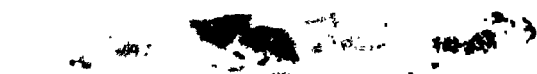
Corner¹¹ correlated the histologic changes at various stages of autolysis and necrosis with the degree of chemical change in the tissue. In the normal spleen about 5.7 per cent of the total nitrogen is in the water soluble fraction in the form of ammonia compounds, aminoacids, peptones, purin bases, gelatin, etc., while 94.3 per cent of the nitrogen is in an insoluble, coagulable, precipitable form as proteins, nucleoproteins, and other insoluble organic nitrogen combinations.

At the stage of autolysis, *in vitro*, when pyknosis is marked, 7.4 per cent of the nitrogen is soluble. When karyorrhexis and karyolysis are marked, the water soluble nitrogen has increased to 26.5 per cent of the total nitrogen, due mainly to amino

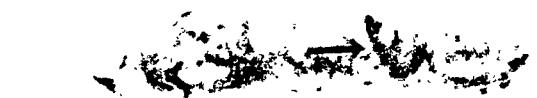
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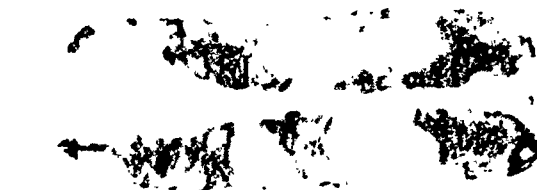
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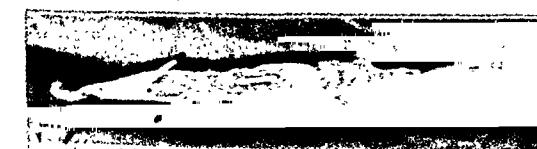
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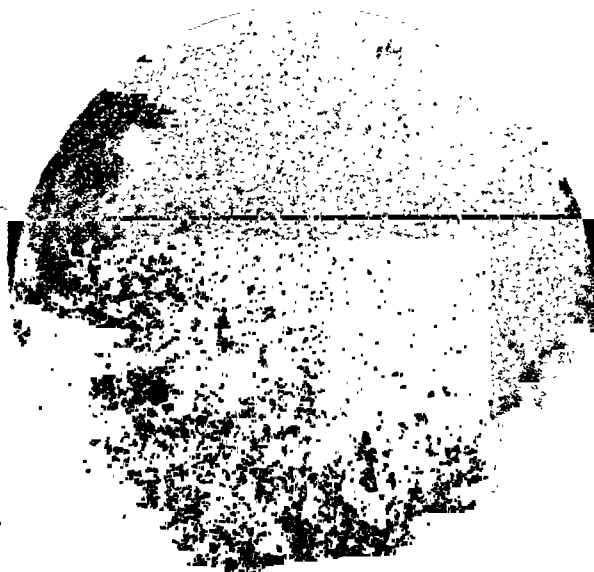
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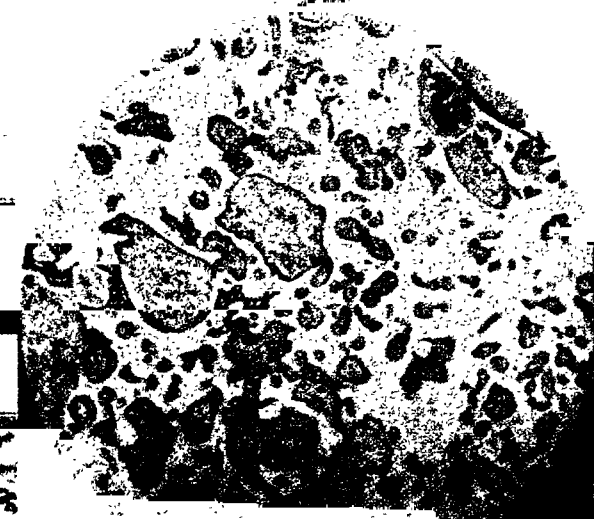
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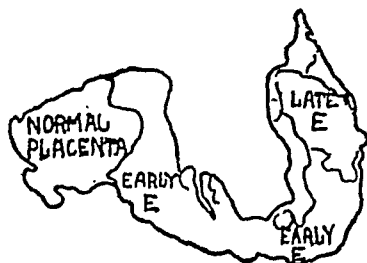




11. Onset acute toxemia at 34th week (early D Infarct); pre-eclampsia at 36th week (late E Infarct). Labor induced.



12. Onset acute toxemia at 38th week (late E Infarct); pre-eclampsia within 10 to 14 days; labor induced; some hemorrhagic tendency; hematoma in perineal repair.



14. Acute toxemia at 32nd week (late E Infarct), terminating in severe abruptio 7 to 10 days later (extensive early E Infarct, involving four-fifths of placental strip throughout midportion, with indentation and separation of placenta); stillborn child.



15. Onset acute toxemia 35th week, terminating in abruptio ten days later (early E Infarct).



16. Excavated lesion (F), probably due to simple hemorrhage from ruptured villous vessel without infarction; subsequent absorption of blood, leaving open area.



18. Old simple hemorrhage represented by fibrin (G), with surrounding lighter anemic zone of compressed healthy villi, simulating infarction.



20. Transparent gelatinous area (H) resulting from incomplete clotting of a simple hemorrhage.

13.

Photomicrograph showing early "E" type of infarct. Acute necrosis of villi, pyknosis, open intervillous circulation. No disintegration of villi and no areas of types "A," "B," or "C." Case of very acute eclampsia.

17.

Photomicrograph of old hemorrhage (Fig. 18) within placental substance showing adjacent zone of living compressed villi. Note almost complete obliteration of intervillous spaces.

19.

Photomicrograph showing more recent hemorrhage with diffuse infiltration of blood between living villi, simulating type "E" infarct, grossly, but not as sharply defined.

acids, peptone, and simple nitrogen derivatives. When microscopic changes have practically ceased and the tissue appears to be disintegrated, the soluble nitrogen has increased to 30.3 per cent. The first products of protein disintegration are, therefore, the most toxic and with advanced cleavage the toxicity lessens.

The early form of Infarct *E* (Figs. 14 and 15) must be recognized almost solely by its dark, almost black color, and definite demarcation. The infarction is so early that disintegration has not occurred and the lesion still has the spongy consistency of normal placenta. It is responsible for the more fulminating cases of preeclampsia, eclampsia and abruptio placentae. Young,² who was the first to emphasize the relationship between placental infarcts and eclampsia, stressed the fact that the color change in some of the most acute infarcts may be so slight that it is very likely to be overlooked.

The villi show distention of many of the capillaries, some of which may be ruptured, with extravasation of fetal blood, forming soft black clots within or near the infarct. Various degrees of pyknosis, karyorrhexis, and karyolysis may be seen (Fig. 13).

Infarcts *D* and *E* may result in either abruptio placentae or eclampsia. The tendency to abruptio is greater if the infarct is exposed on the maternal surface of the placenta, thereby concentrating the effect of histamine on the adjacent decidual sinuses with resulting rupture, extravasation of maternal blood, and separation of the placenta.

If the case is one of abruptio, the causative infarct is almost invariably found underlying an indented, compressed area or hemorrhage on the maternal surface. One of the most important factors in the prognosis for the fetus, is the location of this infarct. If it is near the margin of the placenta, very little separation occurs and the fetus may survive (Fig. 10), but if it is near the center of the placenta (Fig. 14), the extravasation tends to separate the placenta and the fetus dies.

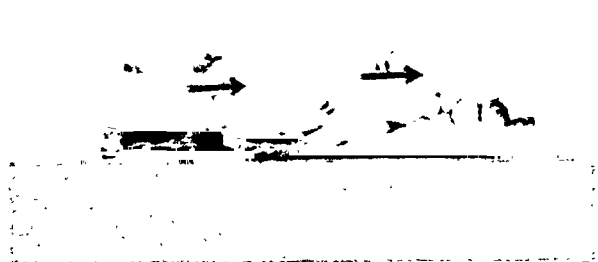
To Summarize.—Lesions *A*, *B*, *C*, *D* and *E*, are true infarcts, characterized by progressive increase in the rapidity of infarction. Grossly, the more rapid the infarction, the less conspicuous the lesion, the less firm the consistency, the darker the color and the greater the toxicity. Microscopically, the more rapid the infarction, the more open the intervillous circulation, the less apparent the intervillous thrombosis, and, except in the most acute stage, the greater the disintegration and loss of staining power of the villi. The range of color, due to change in the hemoglobin, is from very dark purple-black in Infarct *E*, to brown in *D*, to brown-yellow in *C*, to yellow in *B*, and to white in *A*. The size and number of the infarcts bear a definite relation to the severity of the toxemia.

In addition to the above described infarcts, there are several other lesions which are frequently seen but which have no specific relation to toxemia.

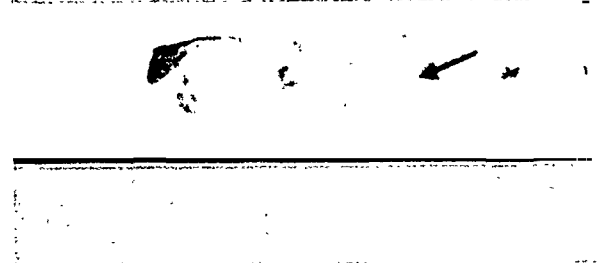
Lesion *F* (Fig. 16) is recognized as an excavation in the placental substance. The appearance suggests a forcible pushing aside of the villi, presumably by a sudden outpouring of fetal blood from a ruptured villus. If the fetal and maternal blood are compatible, the extravasation remains fluid and is soon removed through the intervillous circulation, leaving an excavated area which often shows a narrow rim of compressed placental tissue. This border simulates infarction but shows no microscopic evidence of necrosis (Fig. 17).

Lesion *F* occurs with great frequency in both normal and pathologic placentas and has no significance as to toxemia. One can merely speculate as to the cause, but we believe the lesion is best explained by the fact that from time to time in the latter months of pregnancy, the fetus, by its own movements or change in position, may compress the cord and cause temporary compression of the large thin-walled umbilical vein. Clinical evidence of this is seen in the temporary marked slowing of the fetal heart tones which may occasionally be heard in the latter months of pregnancy and unassociated with a uterine contraction. The same evidence, but more persistent and of serious significance, is obtained in the second stage of labor, if a coil of cord, around the neck, becomes compressed against the pubic bone. It is possible that the resulting increased distention of the capillaries of the terminal villi may cause some of them to rupture and produce the above described lesion.

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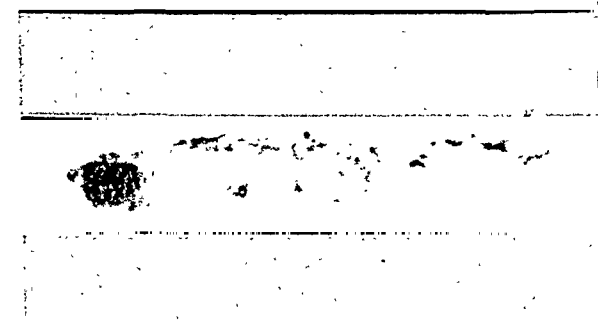
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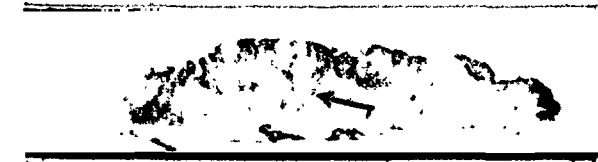
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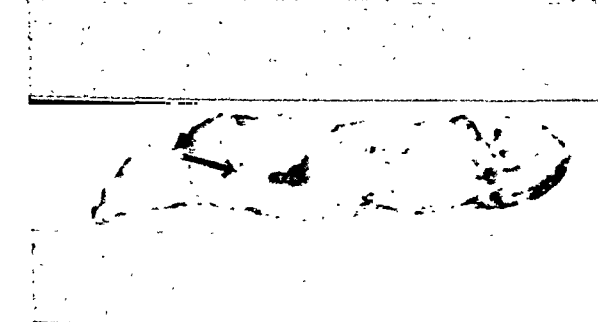
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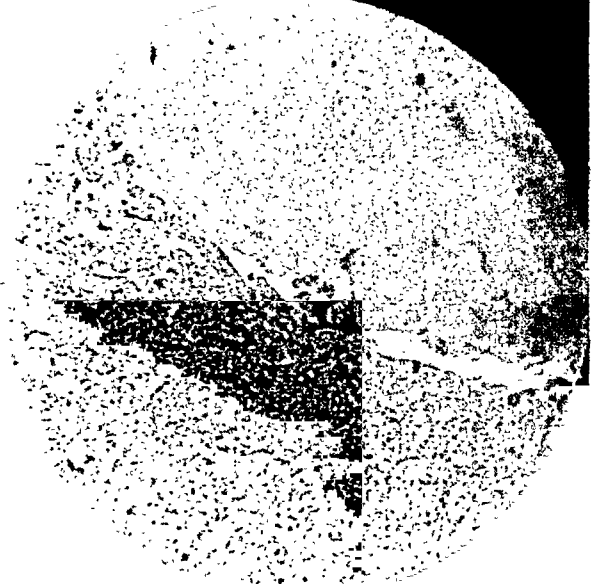
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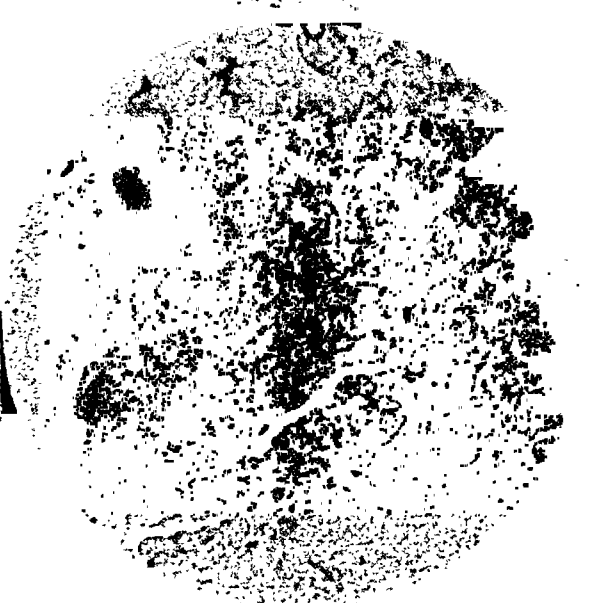


TABLE I

Placentas Showing No Lesions. Three Cases, or A, F, G, or H (Nontoxic Lesions) Without B, C, D, or E (Toxic Lesions)—46 Cases. Total 49 Cases

	PATHOLOGIC DIAGNOSIS	CLINICAL DIAGNOSIS
No toxemia	49	36
Mild or moderate toxemia	0	10
Pre-eclampsia	0	1
Eclampsia	0	1
Abruptio placentae	0	1

TABLE II

Placentas Showing B, With or Without A, F, G or H, But Without C, D, or E. Total, 8 Cases

	PATHOLOGIC DIAGNOSIS	CLINICAL DIAGNOSIS
No toxemia	7	5
Mild or moderate toxemia	1	3
Pre-eclampsia	0	0
Eclampsia	0	0
Abruptio placentae	0	0

that a diagnosis of mild toxemia did not seem justified. Two of these, however, showed slight toxemia—an error of 28.5 per cent. This may have been due to underestimating the toxicity of certain of the B lesions or mistaking small lesions of the toxic E or D type for small hemorrhagic areas of the nontoxic G type.

In this group of 3 placentas (Table III), showing lesions of no greater toxicity than the C type, there was one which showed no toxemia, an error of 33 per cent. Had this particular specimen been saved for re-examination, it is possible the error could have been explained grossly or microscopically.

TABLE III

Placentas Showing C With or Without A, B, F, G, or H, But Without D or E. Total, 3 Cases

	PATHOLOGIC DIAGNOSIS	CLINICAL DIAGNOSIS
No toxemia	0	1
Mild or moderate toxemia	3	2
Pre-eclampsia	0	0
Eclampsia	0	0
Abruptio placentae	0	0

TABLE IV

Placentas Showing D With or Without A, B, C, F, G, or H But Without E. Total, 20 Cases

	PATHOLOGIC DIAGNOSIS	CLINICAL DIAGNOSIS
No toxemia	0	6
Mild or moderate toxemia	14	7
Pre-eclampsia	1	2
Eclampsia	4	4
Abruptio placentae	1	1

In this group of 20 placentas (Table IV), showing lesions of increasing toxicity up to and including D, which is usually associated with pre-eclampsia, eclampsia, and ab-

Lesion G (Fig. 18) is of frequent occurrence and is merely a collection of blood surrounded by normal or slightly compressed placental tissue. If of recent origin, it is black or very dark red in color, but with increasing age and change in hemoglobin, it becomes brown with light striations of fibrin, then yellow and finally dull white in color. Theoretically, the etiology is the same as that of lesion F, but the extravasated blood is probably incompatible with the maternal blood, hence a coagulum results, rather than an excavation.

If lesion G is small and of recent origin, it may simulate lesion E, but the dark area is more diffuse and not so sharply circumscribed, and microscopically the villi do not show necrosis (Fig. 19). If it is old and of larger size, it may simulate Lesion A, but the fact that it may be picked apart as flakes of yellow fibrin serves to differentiate it. If a hemorrhagic area is fresh or recent, one should examine closely for possible adjacent acute infarction, but if yellow or gelatinous the evident age of the hemorrhage argues against an associated acute infarction.

Lesion H (Fig. 20) is recognized as a collection of transparent jellylike material, usually in the substance of the placenta. The appearance strongly suggests it may have originated from an extravasation of fetal blood, similar to Lesion G, but with sufficient incompatibility to form a soft coagulum, but not enough to form layers of fibrin. With absorption of hemoglobin, a transparent gelatinous substance remains. Occasionally one finds gelatinous lesions of a pink color due to unabsorbed hemoglobin, and in which shadows of red blood cells may be seen.

To Summarize.—Lesions F, G, and H are probably due to extravasations of fetal blood from rupture of terminal villous capillaries, due to temporary compression of the umbilical vein. If the fetal and maternal blood are compatible, the collection of blood remains fluid and is drained away, leaving an excavated area (F). With greater incompatibility, the lesion may vary from a transparent jellylike clot (H) to a firm clot (G) which passes through color changes from black to brown, to yellow and finally to the dull white color of fibrin. None of these lesions has any relation to toxemia, unless associated with acute infarction, in which case the hemorrhage is dark.

The relative frequency of the various lesions in this particular series was as follows: Infarct G, 68 per cent; Infarct A, 45 per cent; Infarct D, 38 per cent; Infarct F, 22 per cent; Infarct H, 22 per cent; Infarct B, 20 per cent; Infarct E, 20 per cent; Infarct C, 7 per cent. There were no lesions whatsoever in 3 per cent. Since these were selected cases, the above figures do not represent the natural relative frequency. It is evident that an absolutely normal lesion-free placenta is a rarity. There were only three placentas which showed no pathology.

There is some question as to the accuracy of the figures representing Infarcts E and G. The possibility of error arises from the fact that a small recent hemorrhagic area (G) may simulate an early infarction (late E or early D). In both bases the area is dark, but the hemorrhagic area is more diffuse, not so sharply demarcated from the surrounding normal tissue and more likely to be infiltrated with soft, black clot (Fig. 19). Some of these lesions may be difficult to differentiate without microscopic examination. There is no difficulty whatsoever in recognizing lesions A, B, C, late D, G (large hemorrhage), F, and H.

The following tables represent an analysis of the cases arranged in groups according to the type of infarct, and listed in the order of increasing toxicity from A to E, inclusive. The pathologic and clinical diagnoses are compared and the error in pathologic diagnosis estimated and explained.

In this group of 49 placentas (Table I), there were apparently none of the toxic lesions, B, C, D, or E, yet 10 cases showed mild or moderate toxemia and 3 cases severe toxemia, an error of 26.5 per cent. This was found to be due to mistaking small areas of true infarction (E or early D) for small hemorrhagic areas of the non-toxic early G type, or entirely overlooking a very early acute infarction.

In this group of 8 placentas (Table II), showing lesions of no greater toxicity than the B type, there were 7 in which the yellow color of the lesion was so slight

infarcted area, should, at the line of demarcation, be quite harmless to the surrounding, adjoining villi. Neither can it be visioned how blockage in one or even several maternal arteries at the placental site could deprive the adjacent villi of blood from other maternal arteries, which is free to reach these villi through the open intervillous circulation.

We conceive the basis for toxemia of pregnancy to be laid down early in pregnancy by the physiologic hypercholesteremia of pregnancy, which is exaggerated in women of a hypothyroid endocrine type. In the latter months of pregnancy certain focal changes occur beneath the endothelium and in the walls of the small placental arteries, which are apparently identical with those seen in cholesterol-fed rabbits and in the coronaries of individuals dying suddenly of coronary thrombosis as seen in Figs. 1, 2, 3, and 4.⁷ These changes do not occur along the entire course of the artery but are focal, probably at points of greater stress or where the artery has sustained trauma from fetal movements.

With spontaneous breaking down of the lipoid cells in such a focus, or due to the trauma of fetal movements, the endothelium overlying the focus is broken down and roughened and thrombosis occurs. Acute infarction of the dependent villi results which accounts for the sharp line of demarcation between the normal and infarcted tissue, corresponding to the arterial distribution. Necrosis and autolysis of the villi permits diffusion of poisonous protein split products, probably peptone, guanidine and histamine, throughout the maternal organism. The known pathologic effects of these three poisons apparently explains the symptomatology and pathology of toxemia of pregnancy.^{1, 5}

We note the prevalent tendency to regard toxemia of pregnancy, in some unknown way, as the result of vascular disease of the mother, disregarding the fundamental fact that identical vascular changes, when seen in the male or female, apart from the pregnant state, do not terminate in eclampsia or show the liver or kidney pathology of eclampsia. Three patients in our series had a pregestational vascular disease, but in no case did true pregnancy toxemia develop.

If ophthalmoscopic examination is made, coincident with or very soon after the first clinical manifestations of toxemia, edema, slight rise in diastolic blood pressure and slight albuminuria, one may note an occasional slight localized constriction or spasm in one or more of the retinal arteries. With increasing clinical symptoms and signs, the spasms become more numerous and change from sausage-like to spindle-shaped constrictions, and gradually the entire artery becomes spastic and reduced in caliber.

The evidence indicates that the arterial spasms are the effect and not the cause of the toxemia and are initiated in some way by one of the poisonous products of placental autolysis. Since guanidine is known to produce peripheral vasoconstriction, raise blood pressure,¹² and cause convulsions,⁵ it is probable that arginine, which is present in a relatively large amount in placental tissue, is the probable source of a relatively large amount of guanidine in the course of placental autolysis.

Experimentally, we know that autolysate of placental tissue, if injected into guinea pigs, produces convulsions and death, with liver and

ruptio placentae, we found this particular lesion (*D*) so well defined and of such size or number in 6 placentas, that a pathologic diagnosis of pre-eclampsia, eclampsia, or abruptio placentae was made and verified clinically in each case. In another placenta the lesion seemed to indicate only moderately severe toxemia, but clinically the diagnosis was pre-eclampsia. The lesions in the remaining 13 placentas were small in size or number, hence, a diagnosis of mild or moderate toxemia was made. Six of these, however, showed no toxemia, clinically, and here again a recent nontoxic hemorrhagic area (*G*) was mistaken for a small toxic infarct of the early *D* type, accounting for an error of 30 per cent in the group as a whole. There was essentially no error in the pathologic diagnosis of the 7 severe toxemias.

In this group of 20 placentas (Table V) showing lesions of increasing toxicity up to and including *E*, which is associated with pre-eclampsia, eclampsia, or abruptio placentae of a more acute fulminating type, we found this particular lesion so well defined and of such size or number in 18 placentas, that a pathologic diagnosis of pre-eclampsia, eclampsia, or abruptio placentae was made and verified clinically in all but two cases, an error of 11 per cent. These two cases proved to be mild or moderate toxemia, and the 2 cases diagnosed pathologically as mild or moderate toxemia proved to be clinically nontoxic. Again, the errors were due to misinterpreting the nontoxic hemorrhagic lesion (*G*).

TABLE V

Placentas Showing *E* With or Without *A*, *B*, *C*, *D*, *F*, *G*, or *H*. Total, 20 Cases

	PATHOLOGIC DIAGNOSIS	CLINICAL DIAGNOSIS
No toxemia	0	2
Mild or moderate toxemia	2	2
Pre-eclampsia	6	5
Eclampsia	6	5
Abruptio placentae	6	6

If we group the cases of pre-eclampsia, eclampsia, and abruptio placentae in Tables I, IV, and V, it will be seen that out of 26 clinically proved severe toxemias, 24 were diagnosed by gross examination of the placentas, a correct diagnosis in 92 per cent.

It will also be seen that out of 24 cases diagnosed from gross examination of the placentas as severe toxemias, there were only 2 cases which clinically were not of this type, a correct diagnosis of 91.6 per cent.

We may therefore say that there is a definite association of the more acute types of placental infarcts with toxemia of pregnancy. In other words, if one knows the clinical course of pregnancy in regard to toxic manifestations, it is possible to predict quite accurately the type of infarct that will be seen in the placenta. Conversely, if one examines the unknown placenta, he may describe quite accurately the clinical course of the pregnancy in regard to toxemia.

The prevailing opinion would have it that these infarcts are the result of some unknown toxemia having its origin on the maternal side or from blockage of some of the maternal arteries supplying the placental site—the effect and not the cause of the toxemia.

The infarcts are sharply demarcated, both grossly and microscopically. Thrombosis is present in the great majority of villous capillaries and small arteries in the infarcted area. It is beyond reason that a hypothetical maternal toxin circulating freely throughout the placenta, and powerful enough to cause necrosis and disintegration of all villi in the

cause of toxemia, and is probably due to guanidine as a product of placental infarction and autolysis. Increased guanidine compounds have been demonstrated in the blood of eclamptic patients.

Irving¹⁸ and Peters¹⁹ deny the existence of circulating toxins in eclampsia and attribute the pathology and symptomatology to the ischemia produced by widespread arterial spasm. We do not find the counterpart of the eclamptic syndrome and pathology in cases of essential hypertension or malignant hypertension in the male or female. Bell²⁰ states that the pathology in the kidney supports the view that a soluble toxic substance in the blood is responsible for eclampsia. It has been shown that if poisonous protein split products are injected into the blood slowly, toxic manifestations may be mild, whereas if the same dose is injected rapidly, the effect is severe. Diamond²¹ in a neuropathologic study of five cases of eclampsia which came to necropsy, concluded that the changes in the brain are similar to those present in severe toxic states in which there is a direct action of toxin on the parenchyma.

A study of the behavior of the basal metabolism in the course of developing toxemia of pregnancy, has progressed sufficiently to enable us to state, as a preliminary report, that a sharp rise of 30, 40, or 50 per cent almost invariably occurs at the onset of toxemia. This response is further evidence that toxemia of pregnancy is a true poisoning or intoxication and stimulates the thyroid in a manner similar to other intoxications.

Patterson, Hunt, and Nicodemus¹⁰ in a recent study based on our theory of the fundamental factors of hypercholesteremia, hypothyroidism, cholesterol vascular changes in the placenta, thrombosis, acute infarction, autolysis, and absorption of poisonous protein split products of placental protein, have verified the consistent association of acute infarction with eclampsia and have produced acute placental infarction and convulsions in thyroidectomized pregnant rabbits.

They believe that a hypothyroid mother makes up for some of her deficiency in thyroxin, by taking this substance from the fetus, thereby creating fetal hypothyroidism and hypercholesteremia, with cholesterol vascular changes in the placental vessels, thrombosis, infarction, and damage to the maternal kidneys by the autolytic poisons. They apparently consider the convulsions uremic in character, due to severe kidney damage. The latter part of this concept is not tenable, considering the lack of evidence of impairment in renal function.¹⁴ Furthermore, a theory of abstraction of fetal thyroxin, if applied to the human being, should confer a lessened risk of eclampsia in cases of multiple pregnancy, but we know the risk is considerably increased.

Maternal hypothyroidism is undoubtedly a strong predisposing factor in rendering the patient more liable to toxemia, but the normal hypercholesteremia in patients showing normal thyroid function, in conjunction with the vulnerability of the placental circulation to fetal trauma and focal cholesterol vascular change must still account for a large group of cases.

Biologically, if cholesterol is the framework of the body cell, it would seem that hypercholesteremia of pregnancy is rather a provision to meet the demands of embryonic cell growth, than the result of a chance maternal hypothyroidism.

We believe that the evidence presented in this study indicates that toxemia of pregnancy is due to placental infarction. Further investigation along the line of the biochemical aspects of the problem will undoubtedly clarify not only the exact poisonous protein split products which are involved but also explain certain variations in the clinical

kidney changes similar to those seen in eclamptic patients. We also know that autolysates of other cellular tissues, such as liver, spleen, or kidney, may produce toxic effects but do not produce convulsions. As stated before, we believe guanidine, histamine, and peptone are derived from autolysis of placental tissue, since the effects observed are so similar, clinically, to those seen in eclampsia. However, an initial recent attempt by Dr. Geo. Lewis, in the Department of Biochemistry, to prove this chemically by showing a greater amount of guanidine in the autolysate of placental tissue as compared with that of liver and spleen, has been unsuccessful, due to technical difficulties involved. This experiment, if successful, would constitute very important evidence in favor of the placental origin of eclampsia.

Granting that placental infarction furnishes a sound pathologic basis to explain the occurrence and manifestations of toxemia of pregnancy, we are better able to correlate certain recent lines of research which, up to this time appeared to be suggestive but unrelated.

Smith and Smith¹³ came to the conclusion that the high level of prolactin found in cases of late pregnancy toxemia, as well as the tendency to a low level of estrin, originate in a placental abnormality "which as yet remains unknown." This abnormality is undoubtedly infarction, the existence of which has hitherto been denied. The Aschheim-Zondek reaction is markedly increased in cases of hydatidiform mole and chorioepithelioma. It is likewise increased in cases of toxemia of pregnancy. Apparently the increase in prolactin and follicle-stimulating effect are the result of placental necrosis which is much greater in these conditions than in normal pregnancy.

Priscilla White¹⁴ in analyzing the pregnancies occurring in a series of diabetic women, noted the incidence of eclampsia to be 5 per cent, as compared with 0.3 per cent in a nondiabetic series. In the light of the known high cholesterol values in the blood of diabetic patients, we would attribute the high frequency of eclampsia to more pronounced cholesterol-vascular changes in the placentas of diabetic patients, with resulting increased incidence of acute infarction.

Vorziemer and others¹⁵ analyzed a series of 120 cases of toxemia from the standpoints of body weight, hair distribution, stature, facies, form of pelvis, basal metabolism, and blood proteins. In not one of the series was there significant impairment of renal function as studied by the concentration test and determination of the nonprotein nitrogen of the blood. In 35 patients on whom repeated observations of the basal metabolism were made, 68 per cent had basal rates below plus 10 per cent, which is the lower limit of normal during pregnancy. Ninety-eight per cent of the toxemic patients exhibited one or more of the endocrine stigmas under consideration, whereas only 15 per cent of the normal cases presented any stigmas.

Here again, hyperpituitarism and hypothyroidism are associated with excess hypercholesterolemia, which lays the basis for, and increases the liability to cholesterol vascular changes, placental infarction and toxemia.

Tenney¹⁶ noted a definite increase in the number of villi showing syncytial degeneration, in eclamptic cases as compared with normal cases. This is understood if we realize the toxic effects of the poisonous protein split products of placental autolysis, as they diffuse from the acute infarct through the intervillous circulation to reach the maternal circulation.

Eastman¹⁷ has raised the pertinent question that if we knew what caused the arterial spasms which are so much in evidence in toxemia of pregnancy, we would be near the solution of the actual cause of eclampsia. The clinical and pathologic evidences presented in this study indicate that arterial spasm is an effect and not the

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The authors wish to express their appreciation to Dr. Lee Bivings for preparation of the color photographs.

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DISCUSSION

DR. EDWARD D. ALLEN, CHICAGO, ILL.—Dr. Bartholomew's paper should reopen the question of the cholesterol metabolism of pregnancy in general, particularly in view of the advance in knowledge of endocrine disturbances and the toxemias of pregnancy.

We can add some weight to his statements concerning the high incidence of the toxemias in patients with a lowered sugar tolerance. We are just completing a study of our series of diabetic pregnancies and find about the same incidence of toxemias as he has just cited. We have extended this study to include the non-diabetic glycosurias and find a similar incidence of toxemia. In fact, the transient glycosurias of early pregnancy have come to be a distinct warning for us of the later appearance of toxemia during the last trimester.

There has been an unfortunate choice of laboratory animals in the experiments on cholesterol deposition. The herbivora and the omnivora have different cholesterol metabolism. It might be well to repeat these experiments using carnivora or omnivora, especially the castrate. The castrate deposits larger amounts of cholesterol than the normal animal. This fact may be tied up with the relative quiescence of the ovary in the last half of pregnancy. Certainly atherosclerosis occurs much more commonly after the sex glands have become inactive.

The liver regulates the equilibrium between the free and esterified cholesterol. Parenchymal damage causes a fall in the esterified portion and parallels it. We have not seen so-called histamine shock in patients who did not show marked hepatic damage by the rose bengal liver function test.

In our previous studies of the toxemias the most constant blood findings have been a high total cholesterol and regularly low sugar values. The cholesterol values determined by the Blorr method have varied from 218 to 484. Dr. Dieckmann found values ranging from 128 to 750 with means of 320 mg. per cent and 303 mg. per cent for the pre-eclamptic and vascular renal disease, respectively. We have observed much higher total cholesterol values than these in the nephrotic patients of our medical co-workers, values up to 1,380.

Epstein states that the increased tolerance of nephrotic patients to thyroid medication is due to this elevated plasma cholesterol as they show no evidence of overdosage until these values are lowered.

We have recently begun a study of overweight pregnancies, nontoxic and toxic, with this fact in mind. The results are as yet too premature except to say that they give promise. Many of these women in spite of generally high metabolic rates tolerate doses of thyroid up to 11 gr. a day with no untoward symptoms. We have been unable to explain the reason for these high metabolic rates, although the patients clinically were definitely hypothyroid types.

Deposition of more than the usual amounts of cholesterol in the tissues usually is evidence of cellular injury or disease. Pathologists suggest that cholesterol deposits are evidence of slow death of the cell. Physiologic activity normally seems to determine the cholesterol content of different tissues. Certainly the placenta is a tissue of high physiologic activity which comes to senescence early. If we add to this the still unknown quantity which produces such marked tissue damage elsewhere such as the liver, kidneys, and brain, perhaps we have enough cause for the pathologic lesion of the placenta which Dr. Bartholomew has so convincingly described.

We are still loath to believe that these lesions are mechanical in origin or are the cause of the convulsions. Rather they are still another evidence of the varied character of toxemia which like syphilis affects different tissue aggregates in different individuals, probably according to the laws of constitutional pathology.

picture of toxemia which are probably due to autolysis being suspended at various stages, thus causing peptone or guanidine or histamine action to predominate.

CONCLUSIONS

1. Placental infarcts of the more acute types are definitely associated with toxemia of pregnancy.

2. The hypercholesteremia of pregnancy is the basis for vascular changes in the placental arteries which predispose to infarction.

3. Hypothyroidism and a diet rich in cholesterol-containing foods are important factors in excessive hypercholesteremia.

4. The trauma of fetal movements on the placental arteries in the latter part of pregnancy is not only a predisposing cause of localized cholesterol change in the vessels but also an exciting cause of thrombosis or rupture at the site of such change, with resulting infarction.

5. The high content of arginine in placental tissue is the probable explanation of the specific eclamptogenic character of placental autolysate, through the formation of guanidine.

6. The known pathologic effects of guanidine, peptone, and histamine apparently explain the clinical and pathologic manifestations of toxemia of pregnancy.

7. The results of a gross examination of 100 placentas from both toxic and normal cases, as "unknowns," without knowledge of the clinical history, shows that it is possible to diagnose the occurrence of severe toxemia in 90 per cent of the cases.

8. Conversely, it is possible to predict the type of infarcts that will be found in the placenta, from a knowledge of the clinical history of the pregnancy as to toxemia.

9. With the experience of examining placentas as "unknowns," it has been found possible to establish criteria for an exact classification of placental infarcts and their relation to toxemia.

10. Further study of the effects of cholesterol and the biochemical aspects of placental autolysis, will clarify many of the clinical and pathologic manifestations of toxemia of pregnancy and will undoubtedly throw considerable light on the subject of hypertension and arteriosclerosis.

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TABLE I. CORRELATION OF DIAGNOSIS OF TOXEMIA FROM PLACENTAS WITH CLINICAL DIAGNOSIS

BARTHOLOMEW'S DIAGNOSIS	CLINICAL DIAGNOSIS
1. Moderately severe acute toxemia	Moderately severe acute toxemia
2. Moderately severe pre-eclampsia	No toxemia
3. Fulminating toxemia, possibly eclampsia	Moderate toxemia
4. No toxemia	No toxemia
5. No toxemia	No toxemia
6. Severe pre-eclampsia or eclampsia	Severe pre-eclampsia
7. Prolonged toxemia with acute exacerbation before delivery, possible toxemia	No toxemia
8. Slowly increasing toxemia with abruptio placentae, and exacerbation of toxemia at delivery	Moderately severe toxemia, first diagnosed 5 days before delivery
9. Moderate toxemia, shortly before delivery	Mild toxemia
10. Mild toxemia	No toxemia

the placenta, most of these fetuses do not die from hemorrhage but from suffocation. As a matter of fact, the fetal death occurs rather rapidly and presents changes at autopsy which are definitely characteristic of asphyxia. The hemorrhage in premature detachment of the placenta comes from the mother and not from the fetus. The fetal hemorrhage of course ceases when the fetus dies and its death is due to asphyxia.

DR. THADDEUS L. MONTGOMERY, PHILADELPHIA, PA.—There is no question but what the careful study of the placenta will reveal many lesions which are closely related to health or disease in the mother and vitality or death in the fetus. Thus in long labor with premature rupture of membranes one will find in the secundines the evidences of inflammation, and in many cases of toxemia with elevated blood pressure the placenta contains hemorrhagic and thrombotic lesions or so-called "infarcts." The frequent occurrence of the latter has often raised the question of their significance, and many have undertaken to prove that they are the cause of eclampsia and allied conditions.

With this viewpoint Dr. Bartholomew is apparently in accord, and yet as I have reviewed his previous work and listened to his paper this morning, I can find no very certain proof that these lesions may not be the result of the toxic condition in the mother rather than the cause of it. In fact there are a number of circumstances which point toward the resultive rather than the causative relationship.

The theory which Dr. Bartholomew has presented is dependent upon acceptance of three views of placental physiology: first, that placental villi and chorionic epithelium are dependent upon fetal circulation for their nourishment; second, that degeneration of chorionic epithelium and of villi is preceded by a thrombotic or obliterative lesion in the corresponding fetal vessels; and third, that the subsequent degeneration of placental structures produces a material which upon absorption into the maternal system causes a systemic toxemia.

Contrary to these concepts, we have many points to indicate that the chorionic epithelium receives its nourishment from the maternal lake of blood and is generally independent of the fetal blood for its vitality. Certainly in the first few days of flourishing embryonic growth, it receives no sustenance from fetal circulation, and in the hyperplastic phases of activity in hydatidiform mole and chorioepithelioma fetal vessels are conspicuous by their absence. In fetal death from syphilis when the fetus is macerated and has evidently been retained in utero for several weeks, examination of the placenta usually reveals a healthy condition of the villi and preservation of the chorionic epithelium even though the development of fetal vessels in the villous stroma is obviously limited and the fetal circulation has long been arrested by fetal death.

The changes that take place in the maturing placenta also indicate that the source of nourishment of the plasmido and cytotrophoblastic layers is the maternal blood stream. Witness the contrast of growth of those villi which are in contact

DR. NICHOLSON J. EASTMAN, BALTIMORE, MD.—In response to a request from Dr. Bartholomew we sent him ten placentas which had been soaked in formalin for several weeks, wrapped in formalin gauze and packed in an air tight container. The clinical diagnoses of these ten cases together with Dr. Bartholomew's diagnoses made from examination of the placenta are shown in the following table:

CASE NUMBER	CLINICAL DIAGNOSIS	DR. BARTHOLOMEW'S DIAGNOSIS
1	Pre-eclampsia	Acute toxemia
2	Eclampsia	Acute toxemia; abruptio placentae
3	Pre-eclampsia	Acute toxemia
4	Normal pregnancy	Eclampsia
5	Normal pregnancy	Normal pregnancy
6	Low reserve kidney (very mild)	Acute toxemia, moderately severe
7	Normal pregnancy	Normal pregnancy
8	Normal pregnancy	Severe pre-eclampsia or eclampsia
9	Pre-eclampsia, severe	Eclampsia
10	Eclampsia	Moderate toxemia or abruptio placentae

It will be seen that there were only two serious errors. In Cases 4 and 8, he made a diagnosis of eclampsia; in both of these instances the patients were entirely normal throughout the pregnancy, the highest systolic pressure in one being 118 and in the other 115. There was no toxemia at any time. These errors suggest that the placental lesions upon which he made his diagnosis of eclampsia are not absolutely pathognomonic of that disease. Considering, however, that Dr. Bartholomew had no clinical information about these cases, neither age, parity nor duration of pregnancy, the results in the other eight cases are excellent. In no case with clinical signs of toxemia did he fail to find evidence of the disease in the placenta. And it is interesting to note that his only errors were positive errors, that is, they lay in finding pathologic changes in the placentas of cases that were quite normal clinically.

DR. FRED L. ADAIR, CHICAGO, ILL.—At Dr. Bartholomew's request, we followed the same course as Dr. Eastman described in forwarding unknown placentas to the author. He returned us his diagnosis and description of the placenta without any knowledge as to the case itself from a clinical standpoint. Our clinical studies of the cases were compared with his studies of the placentas, with the following results in the 10 cases. The laboratory and clinical diagnoses check as to the presence of toxemia in 5 of the cases, but as to the degree of the toxemia in only 1, and as to the absence of toxemia in 2 cases.

Dr. Bartholomew's laboratory diagnosis was positive as to toxic states in 3 cases, but clinically our diagnosis was negative in all. In speaking of the presence or absence of toxic states, we admit that a variety of conditions and not a specific toxemia are included; this was accurate in 70 per cent and inaccurate in 30 per cent.

The following tabulation (Table I) shows the correlation between Dr. Bartholomew's diagnosis and our clinical diagnosis.

A number of years ago I made a rather extensive study of the placenta in relation to toxemias and concluded that placental changes were very frequent in so-called toxic states of pregnancy, but that in some cases of toxemia there were no placental changes demonstrable; further, that identical placental changes were to be found in other cases presenting evidence of infection, and in some which were normal. Therefore, while the so-called toxic states of pregnancy produce certain degenerative changes in placental tissue, they were not pathognomonic. Hence the changes in the placenta were not to be regarded as the etiologic factor in the toxemias but rather the result of the toxemia.

Dr. Bartholomew mentioned some of the effects of these placental degenerative changes of the fetus, particularly with reference to premature separation of the placenta. The chronic conditions naturally involve the fetus and do produce death of the fetus. However, in relation to the premature separation or detachment of

STUDIES ON PELVIC ARRESTS*

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INTRODUCTION

THIS report is concerned with the importance of the size and shape of the pelvis in forceps deliveries, especially in regard to the low-medium and medium types. Observations have been made through the study of the pelvis by roentgenologic methods in conjunction with the description of the clinical procedure used to effect delivery from the occipito-anterior, transverse, and posterior positions. Conclusions have been drawn from the degree of ease or difficulty encountered in the mechanics of delivery. At this time interest is directed to the *mechanism used in the forceps delivery in relation to pelvic type* rather than the indications for the operative delivery.

MATERIAL AND METHODS

The size and shape of the pelvis and the fetal-pelvic relationships during labor are visualized in a specially-constructed stereoscope from stereoroentgenograms obtained according to the technic illustrated in Fig. 1. During the last six years a *selected* series of approximately 3,000 roentgenologic case studies have accumulated at the Sloane Hospital for Women and the Department of Radiology of Presbyterian Hospital, most of which have been obtained with this technic. For the purpose of this report, 500 cases have been chosen from this selected material and divided into five groups according to the method employed for delivery, namely spontaneous delivery of the average-sized infant (3,200 gm. or over), low forceps, low-medium forceps, medium forceps, and cesarean section. In order that the observations may be as significant as possible, these case studies were chosen by the consecutive pulling of films from the roentgen filing cabinets, beginning with the more recent cases and working through the series until 500 were obtained.

The architectural characteristics of the pelvis were studied in the precision stereoscope and classified according to a classification of pelvises previously described by us.^{1, 2} The anteroposterior diameter and widest transverse diameter of the inlet, the interspinous and intertuberous diameters were measured by means of the precision stereoscope. Each case study was analyzed in a uniform manner. This method of analysis of pelvic capacity is illustrated diagrammatically in Fig. 2.

The upper pelvis refers to the space between the plane of the inlet and a plane parallel to it at the level of the ischial spines. The mid-

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with the rich blood supply of the decidua basalis and the attenuated blood vessels of the decidua capsularis. The resultant development is the thick succulent placenta at one site and the atrophic chorionic layer at the other, with a band of degenerated villi demarcating the two at the margin of the placenta.

And finally, if degenerated villi cause toxemia, why do we not uniformly have profound states of poisoning in missed abortion, retained dead fetus, with degenerated placenta, with placental necrosis and death of one fetus in binovular pregnancy.

Some time ago I published a study of the immediate and remote effect of small and large areas of premature placental detachment and pointed out that even in very recent separation necrosis of the placental villi and local chorionic epithelium takes place very rapidly, and this in instances where the general vitality of the fetus is unimpaired and its circulation active.

Aside from the work of Browne, little has been done experimentally to shed light upon the etiology of placental infarcts. The subject is a difficult one to deal with experimentally, but until something more is accomplished along that route the cause and the significance of necrosis of the placenta must remain obscure.

DR. BARTHOLOMEW (closing).—I am glad that Dr. Montgomery brought up the subject of intrauterine fetal death, which has been a puzzle to me in connection with this theory. Theoretically, if a baby dies in utero the placenta should die with it. Why does the patient not have fulminating toxemia at once?

I have studied these placentas, trying to explain why this does not occur and I cannot, as yet, explain it unless in the whole retroplacental area, with death of the baby, there is a shutting off or thrombosis of the retroplacental circulation.

Some work later on may be done to explain this apparent contradiction. But to my mind it does not weaken the evidence that I have seen over this period of years, of the close connection between infarcts and toxemia of pregnancy. It is so consistent that I cannot escape the conclusion that there is a definite association of infarcts and toxemia.

Objection has always been made to the idea that placental infarcts are the source of the toxemia rather than the effect. According to this, one would have to presuppose the existence of a hypothetical toxin circulating in the mother's blood, which would be capable of producing an area of infarction in the placenta.

If our conception of the placental circulation is correct, it seems inconceivable to me how a maternal toxin could have a selective action on any certain group of villi. As I showed in some of these microscopic sections, the intervillous circulation is entirely open, not only adjoining the infarct but within the infarcted area, yet these villi are necrotic, while just across the margin of the infarct we see healthy villi. Furthermore, the vessels of the necrotic villi in the infarcted area show thrombosis. It would seem that the vitality of the villi is dependent mainly on the villous rather than the intervillous circulation.

Furthermore, it has been suggested that placental infarcts result from shutting off of the maternal blood to a certain part of the placenta. Here again, one cannot conceive how an infarct could have its origin in this manner, since intervillous blood is free to reach this area from other directions.

The apparent mistakes which were made in the diagnosis of unknown placentas, furnished by Drs. Adair and Eastman, lead me to mention one fact which we have come to recognize. In the course of prenatal observations the findings on the last visit, perhaps a week or ten days previous, may have been normal. However, on admission to the hospital, in labor, we may be surprised to find an elevated blood pressure and albuminuria, due to an acute toxemia which has developed in this short time interval. Hence, if the patient is not given a final check-up in labor, the placental findings may seem to be incorrect.

inlet and through the interspinous diameter (Fig. 2, *A* and *B*). All anteroposterior diameters below the inlet are thus divided into two parts, an anterior sagittal diameter and a posterior sagittal diameter. Hitherto the terms *anterior* and *posterior sagittal diameters* have been used to define the distance between the under-surface of the symphysis and the midpoint of the intertuberos diameter (anterior sagittal) and from this point to the tip of the sacrum (posterior sagittal). We believe these terms can also be applied to the two parts of anteroposterior diameters for each level of the pelvis as divided by the coronal plane (Fig. 2, *B*).

At the inlet the lengths of the anterior and posterior sagittal diameters and the widest transverse diameter vary according to the basic inlet type. Below the inlet, variations in the boundaries of the true pelvis may exist because of changes in pelvic shape as the outlet is approached. Thus the anterior and posterior sagittal diameters at lower levels are affected by variations in the inclination and curvature of the sacrum

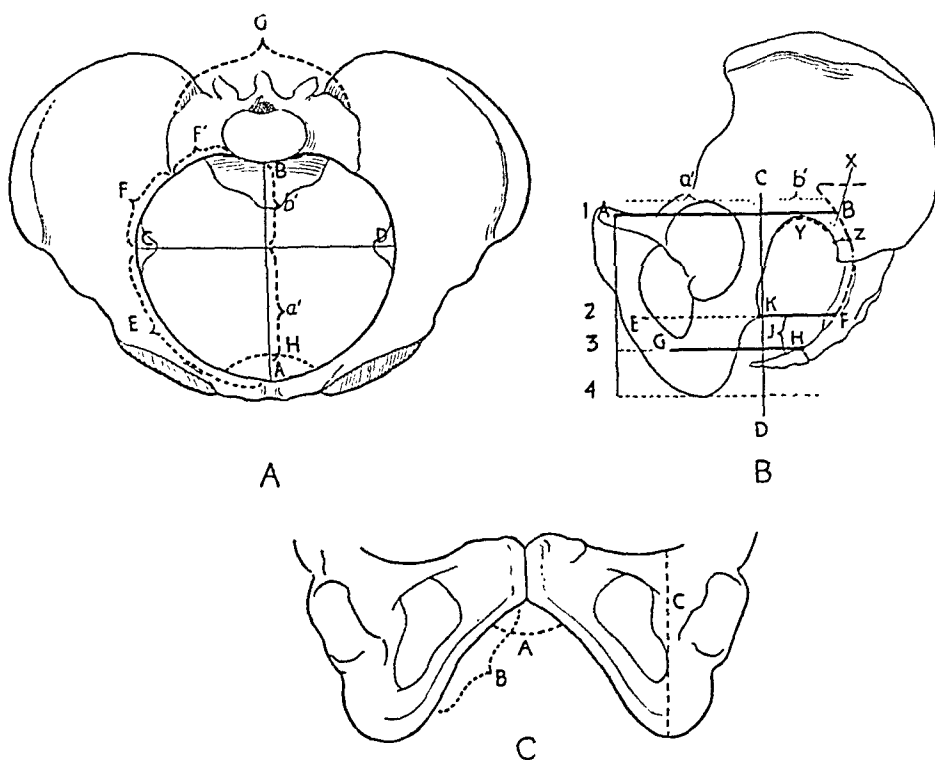


Fig. 2.—*A*, Analysis of pelvic capacity from the inlet view. *CD*, Coronal plane passing through the widest transverse diameter and the ischial spines to form the anterior and posterior segments. *AB*, Anteroposterior diameter of inlet and its two parts; the anterior and posterior sagittal diameter *a'* and *b'*. *E*, Anterior puboiliac boundary of the anterior segment. *F*, Posterior iliac boundary of the posterior segment. *F'*, Sacral portion of boundary of posterior segment variable according to width of sacrum "*G*". *H*, Angle of fore pelvis behind symphysis (retropubic angle) variable according to pelvic type. *B*, Analysis of pelvic capacity as viewed from the lateral aspect. *1, 2, 3, 4*, Parallel pelvic planes. *CD*, Coronal plane through widest transverse diameter of inlet and the interspinous diameter at right angles to the parallel pelvic planes. *AB*, Anteroposterior diameter of inlet with the anterior and posterior sagittal diameters *a'* and *b'*. *Y*, Size and shape of sacrosciatic notch. Variable according to pelvic type. *Z*, Section of ilium which may preserve good length to posterior sagittal diameter (*b'*) in spite of a narrow sacrosciatic notch. *X*, Inclination of the sacrum, the size of the angle subtended by the plane of the inlet *AB* and the upper surface of the sacrum. *KF*, Posterior sagittal at level of ischial spines. *GH*, Anteroposterior diameter of outlet in front of the sacral tip. Note the level of the sacrococcygeal platform to the plane of the spines at *J*. *C*, Analysis of pelvic capacity, front view. *A*, Angle of subpubic arch. Variable in size and shape. *B*, Variations in curvature of pubic rami. *C*, Depth of true pelvis. (Courtesy of Am. J. Roentgenol.)

pelvis extends from the plane at the level of the spines to another parallel plane at the level of the lower border of the last sacral vertebra. The shape of this latter space is most important, especially in difficult forceps operations. The lower pelvis or outlet space lies between this third plane and another plane parallel to it at the level of the intertuberous diameter. These levels are somewhat similar to the four parallel planes of Hodge.³

The pelvis is divided into an anterior and posterior segment by a coronal plane passing through the widest transverse diameter of the

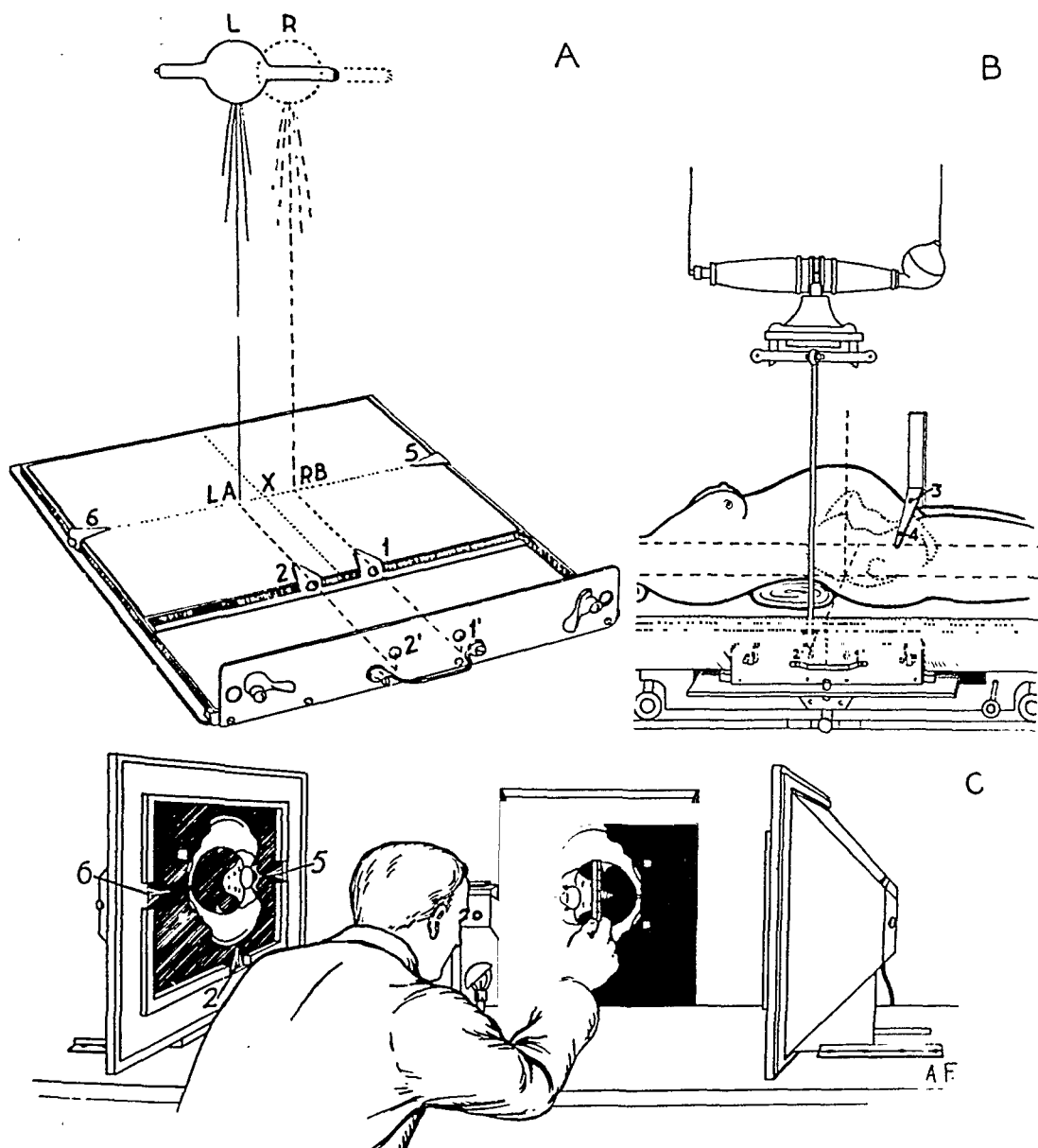


Fig. 1.—A, The cassette frame to mark the films for placement in the viewing box of the precision stereoscope (Fig. 1, C). The cassette frame is placed over the cassette on the cassette tray and fixed by lugs to the side of the x-ray table (see Fig. 1, B) 1' and 2'. With each shift the target moves along the line joining 5 and 6. For each exposure the target bears a perpendicular relationship to either 5 and 2', or 1, 1'. B, The patient supine on the x-ray table with the lumbosacral pad in place. The target is centered just above the mid point of the line joining the anterior-superior iliac spines. Known marker 3 and 4 is suspended just free of the abdomen above the symphysis. C, The viewing surface of the precision stereoscope. The image of the arrow tips 5 and 6 and 2 and 1 are made to superimpose over corresponding lines marked on the celluloid edge of the viewing box. The complete examination also includes a 45 degree angle view of the subpubic arch and a lateral view of the pelvis. (Courtesy of the American Journal of Roentgenology and Thomas Nelson & Sons.)

3. The influence of the lower sacral variations.
4. The relationship of the use of poor mechanics during delivery to stillbirth.
5. The question of disproportion between head size and pelvic size.

THE TYPE OF PELVIS ASSOCIATED WITH VARIOUS METHODS OF DELIVERY

The frequency of occurrence of pelvic types in regard to the method employed for delivery is shown in Table I. The most significant fact revealed by this table is the decrease in gynecoid forms and the marked increase in android forms from the spontaneous to the cesarean section group. The efficiency of the anthropoid pelvis is demonstrated by the decrease in incidence of this type and its borderline forms from the spontaneous to the cesarean section group. In 500 cases four rachitic flat pelvis were noted, all in the cesarean section group.

Average measurements on a group of anthropoid, gynecoid, or flat pelvic types will show a ratio between the anteroposterior and the widest transverse diameters which indicate a long narrow oval, a round, or a transverse oval shape. The characteristic wedge-shaped appearance of the android type, however, is not shown by the ratio between these diameters. Accordingly, in this study, no attempt has been made to compute average measurements, since the results would not be significant in revealing pelvic shape.

TABLE I. DISTRIBUTION OF PELVIC TYPES ACCORDING TO THE METHOD OF DELIVERY

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	GYNECOID	ANDROID	ANDROID GYNECOID	GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	RACHITIC FLAT	NUMBER OF CASES
Spontaneous	10	15	9	37	10	8	5	4	2	0	100
Low forceps	16	15	10	32	16	5	3	2	1	0	100
Low midforceps	13	10	12	12	21	14	5	9	4	0	100
Midforceps	12	2	12	15	35	9	6	8	1	0	100
Cesarean section	11	5	9	12	41	7	3	6	2	4	100
Total											500

The smaller the pelvis, the greater is the chance of obstetric difficulty. This well-known fact is evident in Tables II to VI which show an increased frequency of small diameters from the spontaneous to the cesarean section group. But this high frequency of occurrence of small diameters in low-medium and medium forceps cases shows that small diameters do not preclude the possibility of safe delivery through the natural passages. Safe delivery, under such circumstances, may depend upon the efficiency of the forces of labor or the use of mechanical skill in operative deliveries when the pelvis is abnormal. It is for this reason that interest is directed toward pelvic shape in relation to recognized obstetric maneuvers.

Tables II to VI also show that pelves of various types may be associated with a small pelvic diameter. Flat pelves with an antero-posterior diameter of 10 cm. are commonly found in the spontaneous

behind and the inclination of the symphysis and pubic rami in front. Transverse diameters from the inlet to the tuberosities of the ischium are influenced by the slope of the side walls of the pelvis, the length of the ischial spines, and the size and shape of the subpubic arch (Fig. 2, A and C).

The terms "lower anterior pelvis" and "lower posterior pelvis" are frequently used in the descriptions which follow. The lower posterior pelvis refers to the space above the sacrococcygeal platform (*H* in Fig. 2, *B*), while the lower anterior pelvis (or outlet space) refers to the space in front of and below the sacral tip or, more precisely, to the interval between the plane of the sacral tip and the plane of the intertuberous diameter.

The significant anteroposterior diameter of the outlet space extends forward as the third parallel plane into the free space of the subpubic arch (*GH*, Fig. 2). The significant transverse diameter of the outlet space extends between the posterior inner margins of the ischial tuberosities.

At and below the level of the ischial spines the following diameters are important:

1. The level of the sacrococcygeal platform below the ischial spines. See *H*, Fig. 2*B*. (This represents the vertical height between the plane of the spines and the plane of the sacral tip.)
2. The posterior sagittal diameter of the plane of the sacral tip. (See Fig. 2*B*.)
3. The interspinous diameter. Long narrow spines alone are not as significant in decreasing the available space at this diameter as when associated with an inward bulging of the ischium. (See Fig. 2*A*, *c*, *D*.)
4. The intertuberous diameter. (See Fig. 2, *C*.)

The above anatomic approach considers the pelvic cavity from inlet to outlet as a parallelogram, being as deep behind the pubis as in front of the sacrum. This means that the anterior depth of the pelvis includes both the height of the symphysis and the length of the rami.

The subpubic arch was studied in regard to the size of the arch and the length of the interspinous diameter.

It must be appreciated that the 500 cases upon which this report is based are *selected* material. During the investigation on pelvic type and the mechanism of labor, a series of consecutive admissions to the antepartum clinic were studied. In most instances, however, the roentgenologic examination was requested because the obstetrician either suspected the presence of an abnormal pelvis from clinical examination or was desirous of studying the pelvis after some form of difficulty had been encountered during labor. As a result, a statistical review of this material is not comparable to the frequency of occurrence of obstetric difficulty upon the basis of consecutive deliveries. Nevertheless, the case studies chosen serve the purpose to determine:

1. The frequency of occurrence of pelvic types in relation to the method used to effect delivery.
2. The type of pelvis and the mechanism commonly found in the successful use of certain well-recognized obstetric maneuvers with the obstetric forceps.

TABLE V. DISTRIBUTION OF SMALL DIAMETERS ACCORDING TO PELVIC TYPE IN 100 CASES OF MEDIUM FORCEPS DELIVERIES

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	ANDROID GYNECOID	GYNECOID	ANDROID	PLATYPELLOID			NUMBER OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
A.P. diameters of 10 cm.	0	0	1	1	0	2	1	3	0	8
A.P. diameters under 10 cm.	0	0	0	1	0	0	1	0	0	2
Interspinous diameter of 10 cm.	2	2	3	3	4	9	0	1	0	24
Interspinous diameter under 10 cm.	4	1	5	3	0	8	0	0	0	21
Transverse less than 12 cm.	5	0	2	0	0	1	0	0	0	8

TABLE VI.- DISTRIBUTION OF SMALL DIAMETERS ACCORDING TO PELVIC TYPES IN 100 CASES OF DELIVERY BY CESAREAN SECTION*

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	ANDROID GYNECOID	GYNECOID	ANDROID	PLATYPELLOID				NO. OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	RACHITIC FLAT	
A.P. diameter of 10 cm.	0	2	2	1	3	8	1	2	0	0	19
A.P. diameter under 10 cm.	0	0	0	0	1	7	0	4	0	4	16
Interspinous diameter of 10 cm.	2	0	2	1	3	12	0	2	0	0	22
Interspinous diameter under 10 cm.	7	2	4	0	3	15	0	0	0	0	31
Transverse under 12 cm.	6	1	2	0	1	5	0	0	0	0	15

*In Tables II to VI the increased frequency of narrow diameters from the spontaneous to the cesarean section group indicates that the pelvis also decreases in size. In the tables many pelves had more than one small diameter.

interspinous diameter in the medium forceps and cesarean section groups. In anthropoid types the long anteroposterior diameter may compensate for the narrow interspinous diameter, but in android types there is less compensatory space in the sagittal plane or in other regions of the pelvis. These observations show that as pelvic form is so variable any single small diameter is not an index of pelvic capacity. We believe the visual study of stereoroentgenograms represents the best method to employ in the examination of the pelvic architecture, since the narrowest diameter can be seen and measured and the compensatory space can be noted in other diameters.

CLASSIFICATION OF FORCEPS DELIVERIES IN RELATION TO THE MECHANISM OF LABOR

Forceps deliveries are usually classified as low, medium, or high, but each obstetric clinic as a rule makes use of a terminology of its own to designate intermediate types, as, for instance, "low-medium," "high medium," "medium forceps head within the cervix," or "medium forceps with the head partially through cervix."

and low forceps group. Certain android, gynecoid, anthropoid-gynecoid, or android-anthropoid types may, however, have an equally narrowed anteroposterior diameter but may require medium forceps or cesarean

TABLE II. DISTRIBUTION OF SMALL DIAMETERS ACCORDING TO PELVIC TYPES IN 100 CASES OF SPONTANEOUS DELIVERIES OF THE AVERAGE SIZE CHILD (3,200 GM.)

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	ANDROID GYNECOID	GYNECOID	ANDROID	PLATYPELLOID			NUMBER OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
A.P. diameter of 10 cm.	0	0	0	0	0	1	2	0	1	4
A.P. diameter under 10 cm.	0	0	0	0	0	0	0	0	0	0
Interspinous diam. of 10 cm.	4	2	2	1	2	2	0	0	0	13
Interspinous diam. under 10 cm.	3	0	2	0	0	0	0	0	0	5
Transverse less than 12 cm.	2	0	0	0	0	0	0	0	0	2

TABLE III. DISTRIBUTION OF SMALL DIAMETERS ACCORDING TO PELVIC TYPE IN 100 CASES OF LOW FORCEPS DELIVERIES

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	ANDROID GYNECOID	GYNECOID	ANDROID	PLATYPELLOID			NUMBER OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
A.P. diameters of 10 cm.	0	0	0	0	0	0	2	2	0	4
A.P. diameters under 10 cm.	0	0	0	0	0	0	0	0	1	1
Interspinous diameter of 10 cm.	5	2	4	1	0	6	0	0	0	18
Interspinous diameter under 10 cm.	6	2	1	0	1	4	0	0	0	14
Transverse less than 12 cm.	3	1	1	0	0	1	0	0	0	6

TABLE IV. DISTRIBUTION OF SMALL DIAMETERS ACCORDING TO PELVIC TYPES IN 100 CASES OF LOW MIDFORCEPS DELIVERIES

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	ANDROID GYNECOID	GYNECOID	ANDROID	PLATYPELLOID			NUMBER OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
A.P. diameters of 10 cm.	0	1	0	2	0	0	2	3	1	9
A.P. diameters under 10 cm.	0	0	0	0	0	0	0	2	0	2
Interspinous diameter of 10 cm.	4	4	1	4	1	5	1	3	0	23
Interspinous diameter under 10 cm.	5	3	6	2	0	7	1	1	0	25
Transverse less than 12 cm.	5	3	3	1	0	0	0	0	0	12

section to effect delivery. The same principle is noted when a small interspinous diameter is compared to pelvic type and the method employed for delivery. Certain anthropoid types with a small interspinous diameter are found in the spontaneous and low forceps groups. But the android pelvis is commonly associated with an equally narrowed

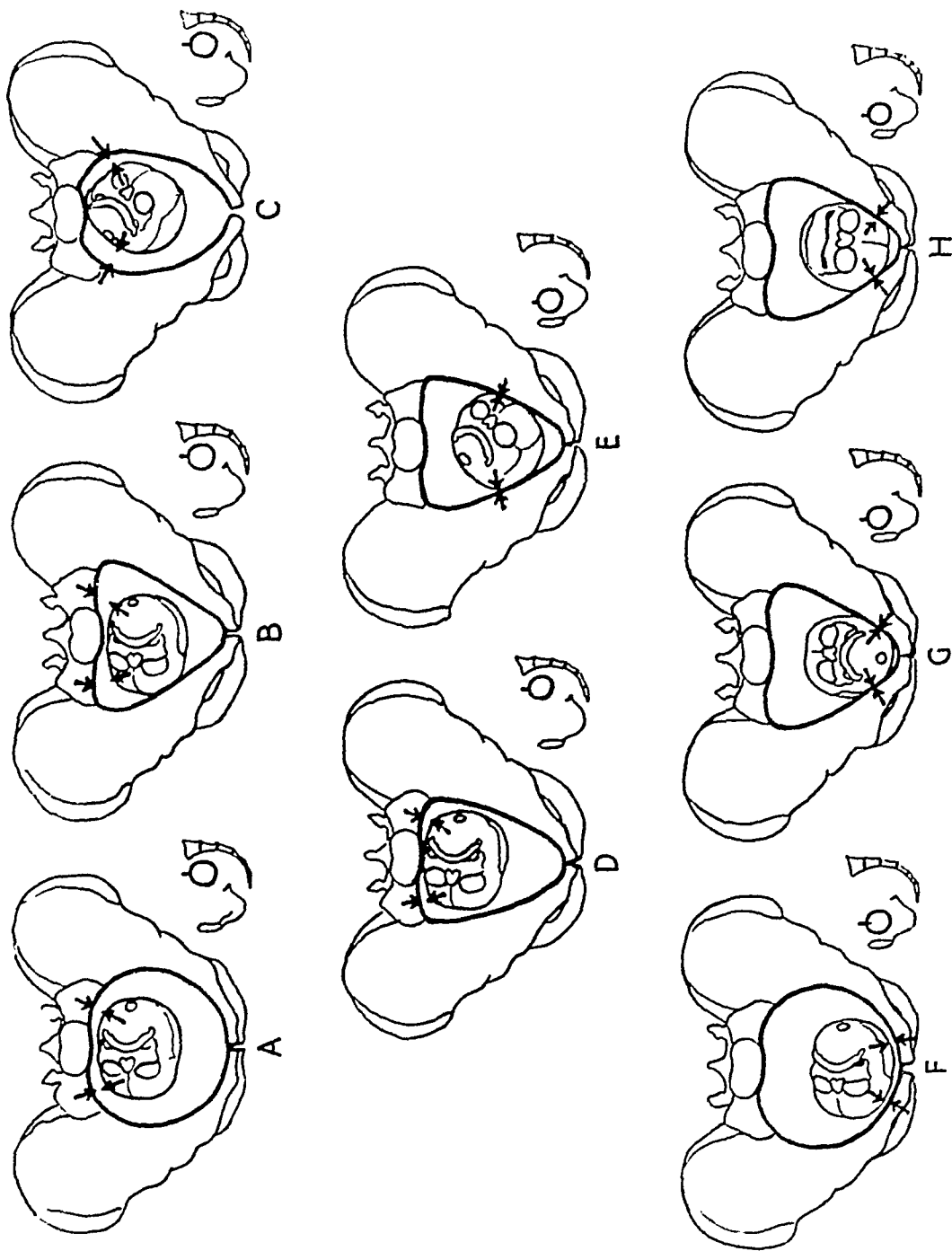


Fig. 3.—Adaptation of fetal head to pelvic shape for variable axes of descent. *A*, Transverse position in gynecoid and platypelloid types caused by the shape of the posterior pelvis as the head descends in an axis through the posterior pelvis. *B*, Adaptation of head to transverse position in the androïd type for the same reason. *C*, Adaptation to the occipitoposterior position or the oblique anterior position in anthropoid type for the same reason. *D*, Adaptation of the head to the transverse position in the android-anthropoid type as head descends through posterior pelvis due to the flat posterior segment. *E*, Adaptation of the head to an occipitoposterior position (or anterior position) as the head descends through axis in the fore pelvis in the android-anthropoid type. *F*, Adaptation of the head to a transverse position with descent through the fore pelvis in pelves possessing a wide angle at the inlet (retropubic angle). *G*, Adaptation of the head to an anterior position in a narrow fore pelvis when the head descends through the anterior segment. *H*, Adaptation of the head to a posterior position in a narrow fore pelvis when the head descends through the anterior segment. As a result of these principles of head adaptation, the obstetric position of the head after engagement has occurred may be quite different from the position which existed before the onset of labor. (Courtesy of Am. J. Roentgenol.)

In this study forceps deliveries are classified as low, low-medium, and medium in type. The high medium forceps delivery was rarely used. On the few occasions (two) in which delivery was effected from this high level, the cases were placed in the medium forceps group.

In the low-medium forceps, arrest occurs on the pelvic floor occasionally with a small amount of caput in sight or with the pelvic floor bulging slightly with each uterine contraction. At this low level the head, as a rule, shows maximum flexion and molding. As a result, anterior rotation, manually or with forceps, can be more easily carried out than at higher levels in spite of the shape of the pelvis. In medium forceps the leading part of the fetal cranium has descended to or slightly below the level of the ischial spines. At this level flexion and molding are usually incomplete. As a result the shape of the upper pelvis, in most instances, exerts its maximum influence in maintaining the original position of arrest and will resist attempts at anterior rotation.

Upon the completion of the study, however, a slight modification of this classification seems indicated, especially if roentgen methods of examination are used to study the mechanism of labor.

In previous reports^{4, 5} it has been pointed out that in certain instances the head may descend through the posterior pelvis close to the sacrum, through the center of the pelvis, or through the anterior pelvis close to the symphysis. The position assumed by the head in its descent depends to a certain extent upon the shape of the particular part of the pelvis through which it passes (Fig. 3). During this investigation no attempt has been made to determine the frequency of occurrence of these axes of descent. But, in the spontaneous and the forceps group numerous instances were noted to show that in inefficient labor in an abnormal pelvis the head descends through the more ample posterior pelvis. In low-medium and medium arrest of the head, the proximity of the head to either the sacrum behind or symphysis in front has complicated the mechanism of forceps delivery. Granted that the axis of descent may guide the head close to the symphysis or to the sacrum, it follows that arrest may occur with the head close to the symphysis in one case or closer to the lower sacral region in another. For this reason it is suggested that, when the position of arrest in relation to the symphysis or sacrum can be accurately ascertained by clinical or roentgenologic methods of examination, the type of forceps operation be classified as "low-medium or medium forceps through anterior pelvis" or "low-medium or medium forceps through the posterior pelvis" or by the use of some other equally descriptive term (Fig. 4, A).

With arrest of the head in the transverse position, anterior rotation brings about a mechanical advantage only if the shape of the upper pelvis will allow rotation, or if anterior rotation is advisable from the standpoint of the shape of the pelvis below the level of arrest (Fig. 4B). The act of anterior rotation brings the occiput into the fore pelvis and simplifies the subsequent forceps delivery.

Most experienced obstetricians have encountered cases in which anterior rotation by manual or instrumental methods is difficult or im-

arrest of the head (Fig. 4C). Barton forceps may be used to rotate the head at the level of arrest or to effect descent to lower levels in the position of arrest. If it is desirable to bring the head to a lower level (low-medium or medium forceps head in posterior pelvis *behind*) (Fig. 4A, 3, 5), the head is made to descend by lateral flexion following the curve of the lower sacrum and sacrococcygeal platform. By this act the influence of the posterior pelvis is removed and anterior rotation can be easily accomplished on the inner aspects of the pubic rami or with caput in sight below the subpubic arch.

In anterior positions this principle is utilized by a downward and forward axis of traction which simulates the act of early extension of the head. In posterior positions, if the head has been delivered to lower levels as such, a downward and forward axis of traction brings it close to the symphysis and promotes flexion.

The head may become arrested close to the symphysis or pubic rami in the position designated as low-medium or medium forceps in the anterior pelvis. In these cases, manual or instrumental methods should be used first to elevate the head and then to direct it slightly downward and backward and thereby avoid misdirected force with traction against the fore pelvis (Fig. 4D). These mechanical principles are mentioned frequently in the discussion of individual case studies.

During the accumulation of the large series of roentgenologic case studies at the Sloane Hospital for Women, numerous examples were found which demonstrated to our satisfaction the importance of pelvic shape in the mechanism of labor. This material enabled us to discuss the mechanism of labor in anthropoid, android, and flat types and to describe extreme examples of descent through the fore pelvis or through the posterior pelvis. This present study was undertaken to prove in a statistical manner the correlation existing between the shape of the pelvis and the particular mechanism used to effect delivery. Accordingly, the results were tabulated in an effort to find, for illustration purposes, several types of pelvis with classical mechanisms.

TRANSVERSE ARRESTS

In 48 cases out of 100 medium forceps deliveries, the head was found in the transverse position. The type of pelvis associated with the particular obstetric maneuver employed to effect delivery is shown in Table VII. In 22 instances the delivery was accomplished by the cephalic application of forceps (commonly Barton forceps) to the transverse position with lateral flexion, descent to the pelvic floor in the same position and low anterior rotation. Two types of pelvis are characteristically responsible for the ease of this mechanism—the android with straight side walls and the flat type of pelvis (Fig. 5B). In the android pelvis, resistance to anterior rotation is offered by the flat posterior pelvis. The presence of straight side walls indicates good transverse diameters throughout the lower pelvis. Lateral flexion removes the influence of the posterior pelvis and allows anterior rotation to occur on the inner

possible to obtain. Numerous maneuvers may be used with success, such as pelvic application of forceps to the transverse position, oblique application, a cephalic application of Kielland forceps, or version and breech extraction. In skilled hands good results are obtained by any of these maneuvers. In our clinic, however, we have been favorably impressed by the use of Barton forceps in the treatment of transverse

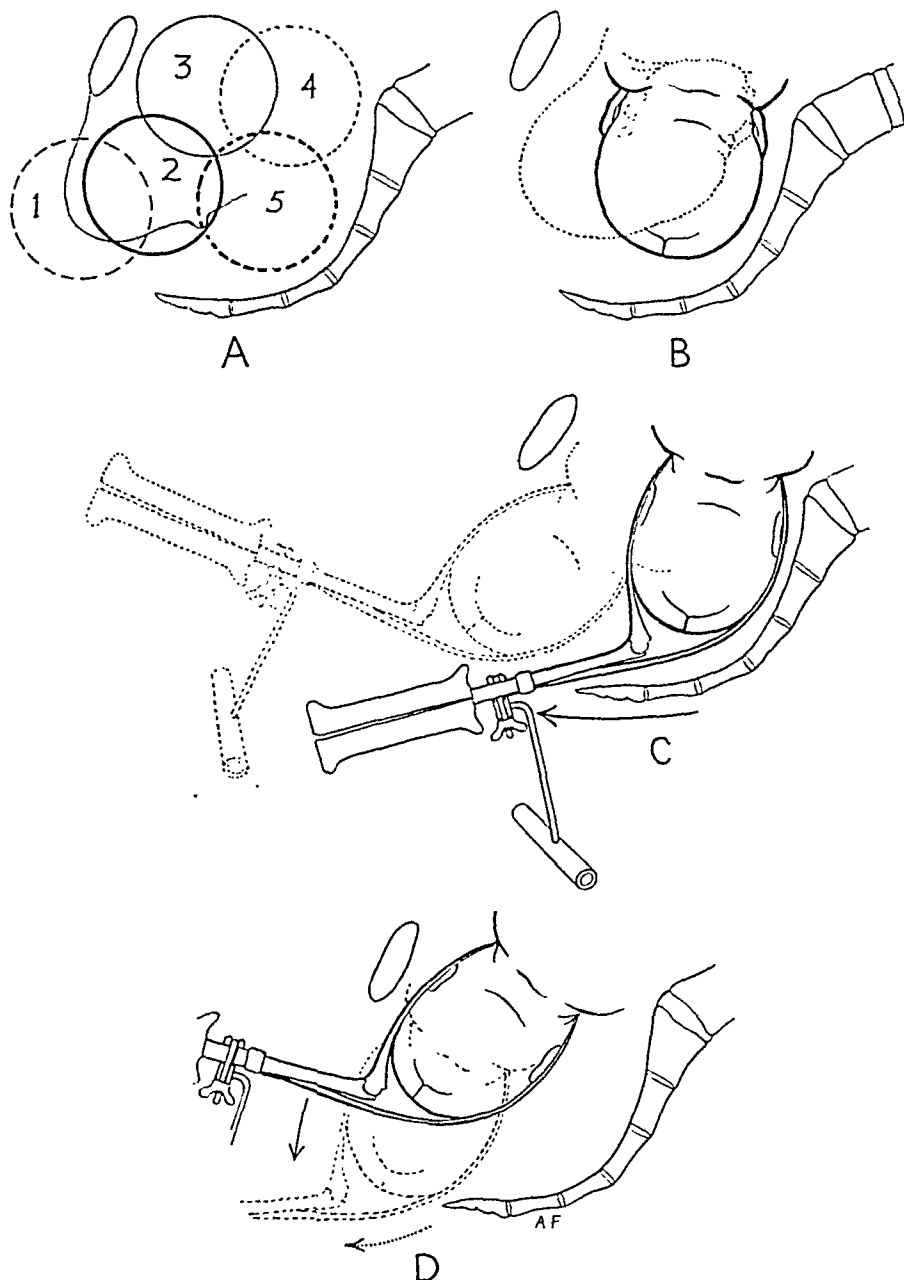


Fig. 4.—A, Classification of forceps from the standpoint of level of arrest. 1, Low forceps; 2, low-medium in the anterior pelvis (in front); 3, low-medium in the posterior pelvis (behind); 4, medium in the anterior pelvis (in front); 5, medium in the posterior pelvis (behind). B, This diagram shows the mechanical advantage of anterior rotation from the transverse position. The occiput approaches closer to the symphysis in the fore pelvis. C, Arrest of the head in the transverse position in the posterior pelvis may be delivered to lower levels in the position of arrest by anterior lateral flexion. Barton forceps are applicable for this mechanism. The head is made to follow closely the curve of the lower sacrum and coccyx. Anterior rotation is accomplished on the inner aspects of the pubic rami or in the subpubic arch. D, Arrest of the head close to the posterior aspects of the symphysis and pubic rami may occur. Forceps may be difficult to apply. The head must be first deviated slightly downward and backward as illustrated, and later laterally flexed as in Fig. 5, D.

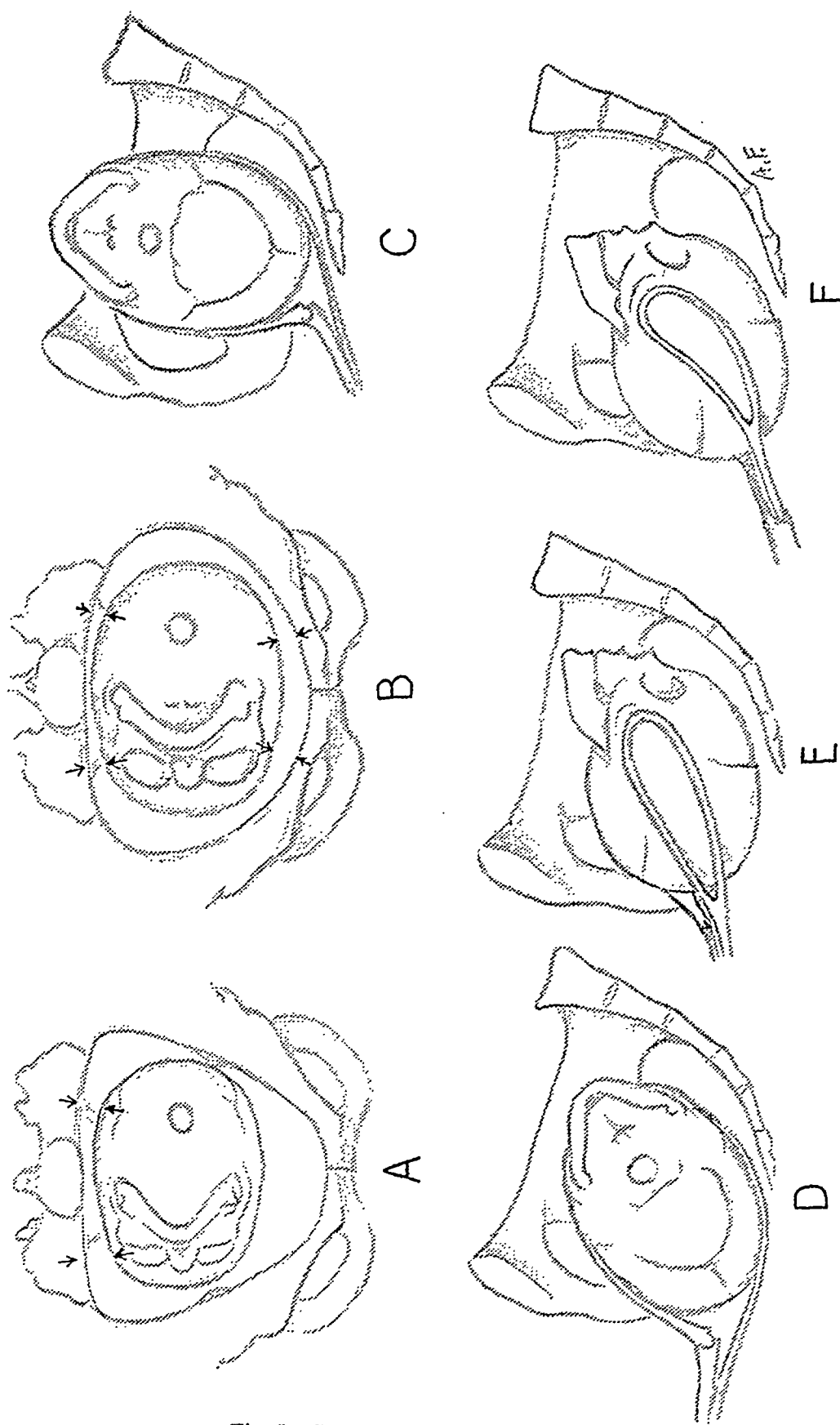


Fig. 5.—See opposite page for legend.

aspects of the pubic rami or at a low level in the subpubic arch. The act of anterior lateral flexion will frequently effect actual descent without the use of strong axis traction force. Barton forceps are used to illustrate this mechanism (Fig. 5*C*, *D*, and *E*). After anterior rotation has been accomplished, Barton forceps are removed and the delivery is terminated by the cephalic application of pelvic curved forceps (Fig. 5*F*).

TABLE VII. DISTRIBUTION OF PELVIC TYPE ACCORDING TO THE MANEUVER USED IN MIDPELVIC ARREST IN THE TRANSVERSE POSITION

(48 in 100 Cases of Midforceps)

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	ANDROID GYNECOID	GYNECOID	ANDROID	PLATYPELLOID			NUMBER OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
Bartons, pelvic or cephalic application in the O.T. with traction to pelvic floor followed by low rotation	0	1	1	4	2	7	2	5	0	22
Anterior rotation with forceps at level of arrest	0	1	4	0	1	4	2	0	0	12
Manual rotation to oblique anterior position with delivery by pelvic curved forceps	1	0	0	0	1	3	0	1	0	6
Spiral anterior rotation by forceps	0	0	0	1	1	5	0	0	0	7
Elevation with anterior rotation and forceps	0	0	0	0	0	0	1	0	0	1
Total										48

In the classical flat pelvis the transverse oval at the inlet is preserved throughout lower levels by means of straight side walls and an average curvature and inclination to the sacrum (Fig. 5*B*). This transverse oval shape is predisposed to a transverse mechanism throughout the pelvis, which becomes more important for ease in labor the greater the degree of flattening, provided the inlet admits the head. Less trauma to mother and child results if the head is made to descend to lower levels in the transverse position, as illustrated in Fig. 5.

The pelvis may show variable degrees and types of flattening. In the true flat pelvis the ischial spines are not conflicting. Nor are they so in the normal pelvis with slight flattening, the so-called gynecoid-flat. The same mechanism occurs in the android-flat pelvis but in this type there may be convergence of the side walls with increased prominence of the ischial spines. Prominent ischial spines may cause lateral sulcus tears if the flattening of the inlet is sufficiently marked to prevent early anterior rotation of the head in an effort to avoid the spines. Separation of the symphysis, stillbirth, a shocked infant, or serious injury to the maternal soft parts has occurred by failure to maintain this transverse mechanism through premature attempts at anterior rotation in certain android and flat pelvic types.

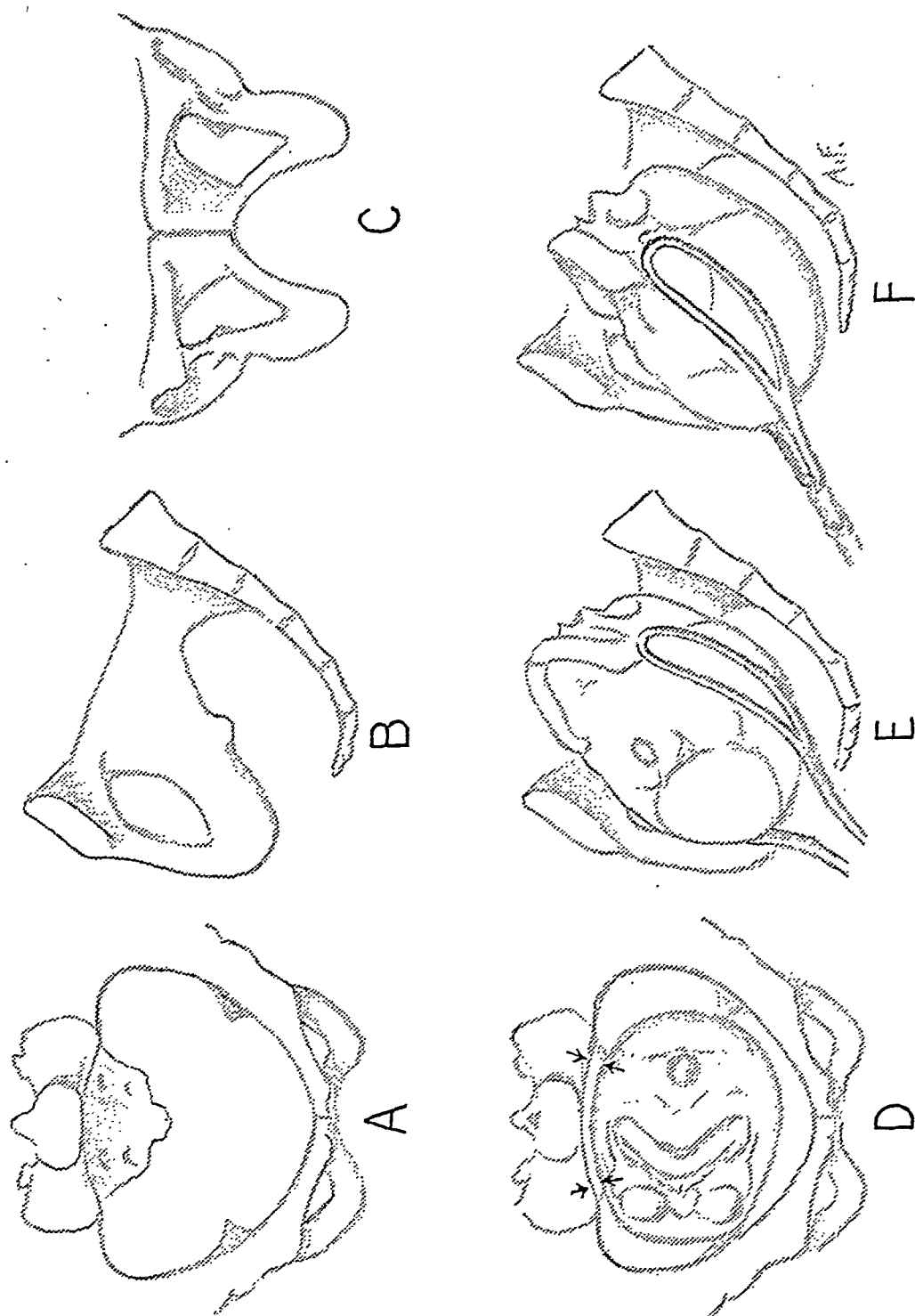


Fig. 6.—The mechanism of spiral anterior rotation in typical android types. A, Inlet view to show the wedge-shaped inlet with converging side walls. B, Lateral view to show the slightly restricted capacity in the posterior pelvis. C, View of the narrow subpubic arch. D, Transverse arrest of the head in midpelvis. The shape of the posterior diameter with converging side walls below require anterior rotation, in order that the biparietal diameter may descend through the intertuberos diameter and the long axis of the head may adjust itself to the sagittal diameter. E, Pelvic curved forceps effect partial rotation and carry the head away from the posterior pelvis by lateral flexion. With descent, anterior rotation continues as the head moves downward and forward. F, Anterior rotation is now completed with the vertex low on the pelvic floor.

Table VII also shows that ease in anterior rotation in transverse arrests of the head usually indicates that there is ample space in the anteroposterior diameter to allow this rotation. There is a decided decrease in flat types when anterior rotation is accomplished by manual or instrumental rotation at the level of arrest.

This table also shows that anterior spiral rotation with descent is commonly associated with a particular type of android pelvis (Fig. 6). The inlet in characteristic android types is wedge-shaped because of the flat posterior pelvis and the narrow angle of the fore pelvis behind the symphysis. There is also a definite degree of convergence with prominent ischial spines and a narrow subpubic arch. Although architecturally the inlet cannot be considered flat, the anteroposterior diameter is usually under average in size and the narrow angle to the fore pelvis creates a flat space in the posterior pelvis through which the head descends. Thus transverse arrest at or slightly below the level of the ischial spines is likely to occur. In the operative delivery the shape of the upper pelvis acts to maintain this transverse position, while the changed shape of the midpelvis, caused by the narrow interspinous diameter, tends to encourage anterior rotation in an attempt to make use of the compensatory space in the sagittal plane at this level. Further descent in the transverse position will bring the head into contact with the restricted interspinous diameter. The correct mechanism in the event of transverse arrest in this type, therefore, consists of anterior lateral flexion associated with spiral rotation. In reality this mechanism consists of anterior lateral flexion which deviates the head toward the pubic rami and away from the posterior pelvis. After this position has been obtained, anterior rotation may be more easily carried out. Occasionally, further descent in the transverse position must be carried out when anterior rotation fails because of the influence of the posterior pelvis at the inlet. As a result, we have found several examples of android types with convergence of the side walls in which delivery was terminated by the use of Barton forceps. In these cases the Barton forceps served to flex the head laterally in the transverse position into the fore pelvis away from the influence of the posterior pelvis. The head descends to a slightly lower level in the transverse position through the widest part of the anterior pelvis in front of the narrow interspinous diameter. Anterior rotation is accomplished at a slightly higher level but according to the principle illustrated for the flat mechanism in Fig. 5. The typical android pelvis (Fig. 6), in our experience, represents the only type in which this spiral anterior rotation with descent is applicable. It is a mechanism which must be used with

Fig. 5.—The mechanism in android types with straight side walls and in the flat type of pelvis. *A*, Anterior rotation is resisted by the opposing forces between the head and the flat posterior pelvis in certain android types. *B*, Anterior rotation is resisted by opposing forces between the head and the posterior and anterior walls of the pelvis in flat forms. *C*, Barton forceps applied to the head. *D*, Descent with lateral flexion. The head follows the curve of the lower sacrum and coccyx. *E*, Anterior rotation is effected at a low level on the inner aspects of the pubic rami or under the subpubic arch after the head has been deviated away from the influence of the posterior pelvis. *F*, Barton forceps are removed and a cephalic application of pelvic curved forceps made for the low terminal delivery.

posterior segment creates a transverse position. If the ischial spines are long and the interspinous diameter is slightly narrowed, the head, not infrequently, descends diagonally downward and forward to pass in front of the ischial spines and utilize the wide intertuberous diameter in the lower fore pelvis. The close approximation of the lateral aspects of the head to the well-formed fore pelvis helps to maintain a transverse position to a low level. In the delivery an attempt must be made first to flex the head laterally away from the symphysis before anterior rotation may occur. In this way one avoids misdirected force with traction against the fore pelvis.

The method of delivery for the low-medium type of arrest in the transverse position and the type of pelvis commonly associated with each maneuver are shown in Table VIII. It will be observed again that when

TABLE III. DISTRIBUTION OF PELVIC TYPE ACCORDING TO THE MANEUVER USED IN DELIVERY IN LOW MIDPELVIC ARREST IN THE TRANSVERSE POSITION

(From 100 Cases of Low Midforceps)

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	ANDROID GYNECOID	ANDROID	GYNECOID	PLATYPELLOID			NUMBER OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
O.T. to floor (Barton forceps) low rotation	0	0	0	0	2	2	2	4	2	12
Rotation to O.A. Manually plus low forceps	0	0	0	1	5	2	1	0	1	10
Anterior rotation with forceps	0	0	0	1	0	3	1	1	1	7
Total										29

low transverse arrest occurs in association with the flat type of pelvis, Barton forceps are used to effect lateral flexion and low rotation. Manual rotation to the anterior position is successful if the pelvis shows compensatory space in the anteroposterior diameter. Occasionally, even in flat types, arrest may occur at a very low level after partial anterior rotation has occurred spontaneously. In these examples a cephalic application of pelvic curved forceps is made to complete the rotation.

It is interesting to note that in no instance was low transverse arrest of the head found in any pelvis possessing an anthropoid or long oval shape. Low transverse arrest in its relationship to the flat pelvis is quite analogous to the low occipitoposterior arrest of the head in relation to the anthropoid type of pelvis.

SUMMARY OF TRANSVERSE ARREST OF THE HEAD

Transverse arrest of the head is characteristically associated with either a flat or an android type of pelvis. In delivery this fact must be appreciated and the transverse position maintained to a low level. If convergence of the side walls exists, then anterior spiral rotation is advisable in android types. Success in manual or forceps rotation at the level of arrest usually implies that an ample anteroposterior diameter is present.

care. Version and breech extraction has occasionally been used to effect delivery in similar cases. It is difficult to study the mechanism in this form of pelvis because in our series such typical android types are found commonly in the cesarean section group. When spontaneous deliveries have occurred in these extreme android forms, adequate labor has molded the head and overcome any bony disproportion.

The examples shown in Fig. 5 illustrate the head close to the sacrum descending through the posterior pelvis, as in the *medium forceps behind* (Fig. 4, A). Other examples will be found in which the head

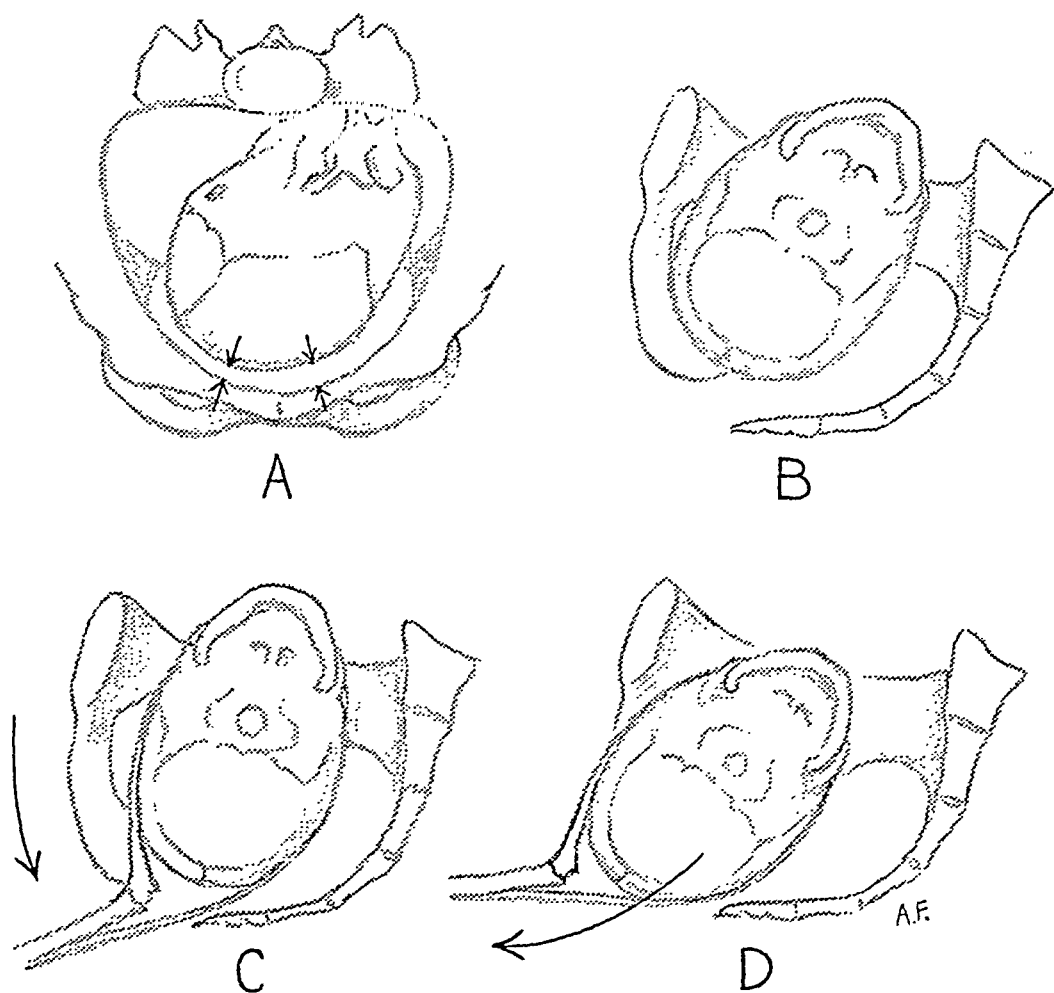


Fig. 7.—The mechanism with arrest in the fore pelvis close to the symphysis and descending pubic rami. A, Arrest in the fore pelvis in the transverse position. Anterior rotation is resisted by the flat surface of the fore pelvis. (The head may present close to the symphysis in any position.) B, Lateral view with transverse position illustrated. The lateral side of the head tends to be close to the posterior aspects of the symphysis. C, The head is dislodged upward and then slightly downward by manual or instrumental methods. D, By lateral flexion the head descends into the outlet and under the subpubic arch, where anterior rotation is carried out.

descends through the fore pelvis close to the symphysis. This type of fore pelvic arrest may occur in any type of pelvis which presents a flat surface to the lateral aspects of the fetal head. The mechanism of delivery is shown in Fig. 7 in association with an android-gynecoid type of pelvis. The android-gynecoid type has compensatory space in the wide, well-formed fore pelvis. In the upper pelvis the shape of the

A flat tendency in the pelvis was present in three cases in which it was noted that a good sacral concavity allowed the occiput to rotate posteriorly (Fig. 9). In these flat types it is obviously desirable to make use of the wide transverse diameter by rotating the head to a transverse position and by maintaining this position to a lower level. The android-anthropoid type was present in three cases in which the flat posterior pelvis resisted anterior rotation. In one extreme anthropoid pelvis, rotation to the transverse position with descent to a lower level in this position represented poor mechanics. In another extreme anthropoid

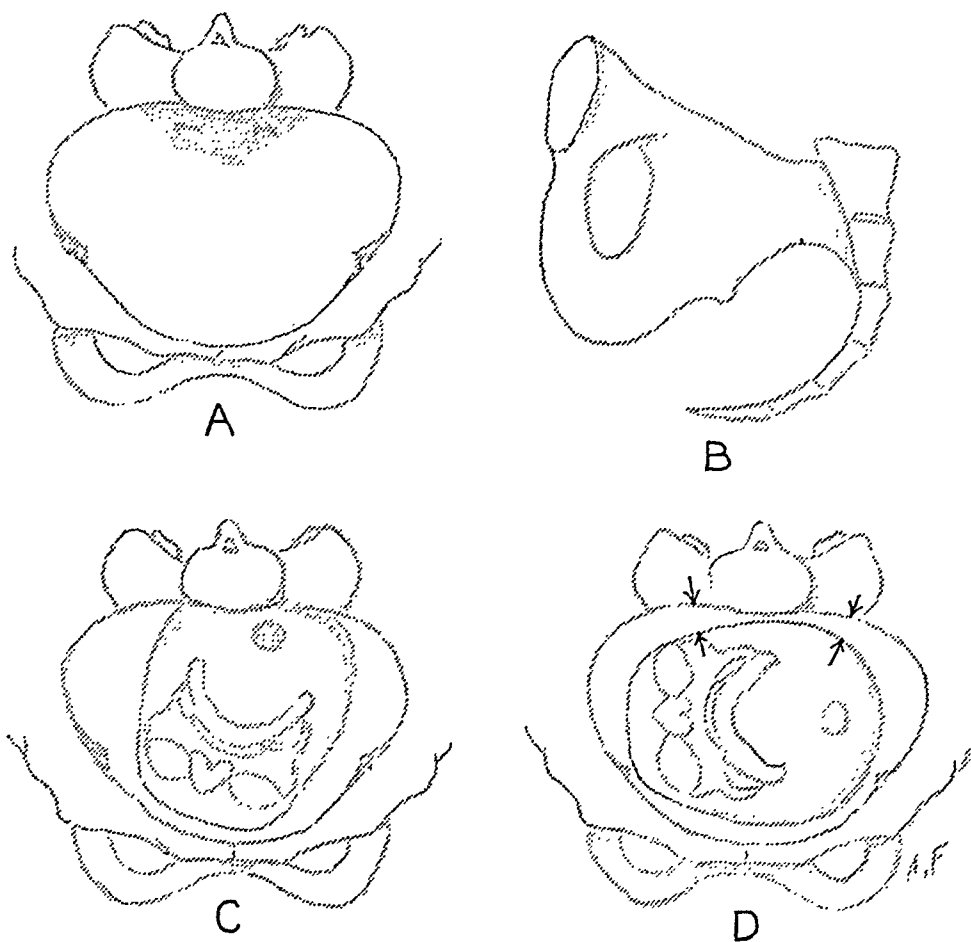


Fig. 9.—The mechanism of arrest in the occipitoposterior position in flat types with a backward sacrum. A, Inlet view. B, Lateral view to show the backward inclination to the sacrum with increased sacral concavity into which the occiput rotates. C, Arrest in the occipitoposterior position in midpelvis. D, As in the android type, Fig. 8, the posterior pelvis prevents rotation of the ovoid head beyond the transverse position. From this position delivery is usually terminated by the use of Barton forceps as illustrated in Fig. 5.

this transverse mechanism was necessary because the outlet had a flat shape owing to a markedly forward sacrum.

A Scanzoni maneuver was performed in four cases with small babies: two in anthropoid types and two in android forms. The Scanzoni's maneuver is too well known to warrant illustration. A pelvic application of forceps to the occipitoposterior position with traction to a lower level was done in four pelvis, three of which were anthropoid types (Fig. 10). As a rule, convergence of the side walls is present further to pre-

POSTERIOR ARRESTS

In 31 cases out of 100 medium forceps deliveries the head was found in the occipitoposterior position (Table IX). In approximately one-half of these cases delivery was accomplished by manual rotation to the transverse position followed by the application of Barton forceps. By lateral flexion and traction the head descended to a lower level in the transverse position, where anterior rotation was performed. The common pelvic

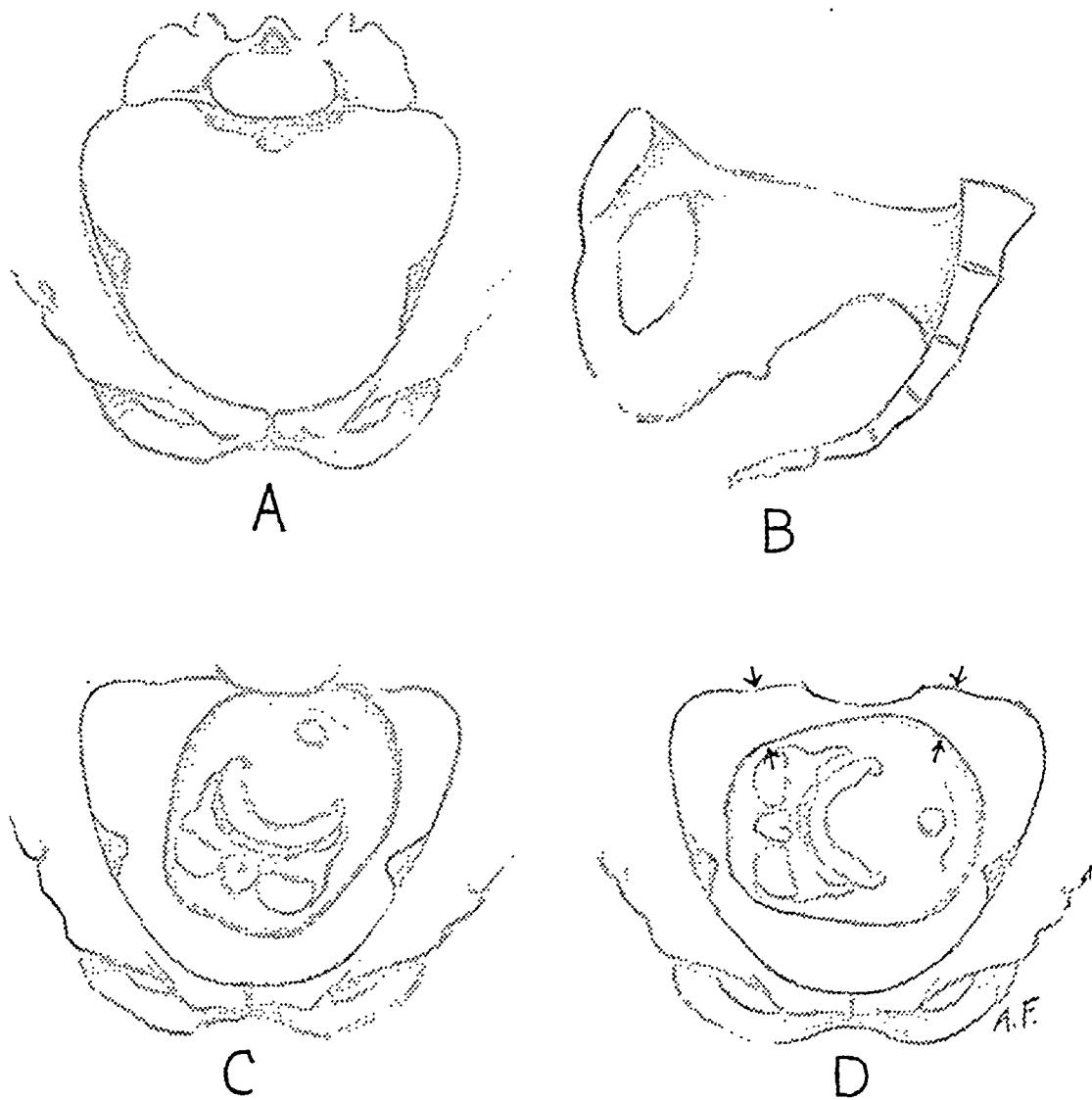


Fig. 8.—*The mechanism of arrest in the occipitoposterior position in android types with slight convergence. A, Inlet view to show the shape of the inlet with slight narrowing of the fore pelvis and slight convergence of the side walls. B, Lateral view. C, Arrest in the occipitoposterior position at midpelvis. The shape of the pelvis aids in causing this position. D, The flat posterior pelvis prevents rotation of the ovoid head beyond the transverse position. From this position the delivery is usually terminated by Barton forceps as shown in Fig. 5.*

type corresponded to the android form with slight convergence of the side walls (Fig. 8). The slight convergence caused the shape of the midpelvis to approach a long oval type. The flat posterior pelvis prevented complete anterior rotation beyond the transverse at the level of arrest.

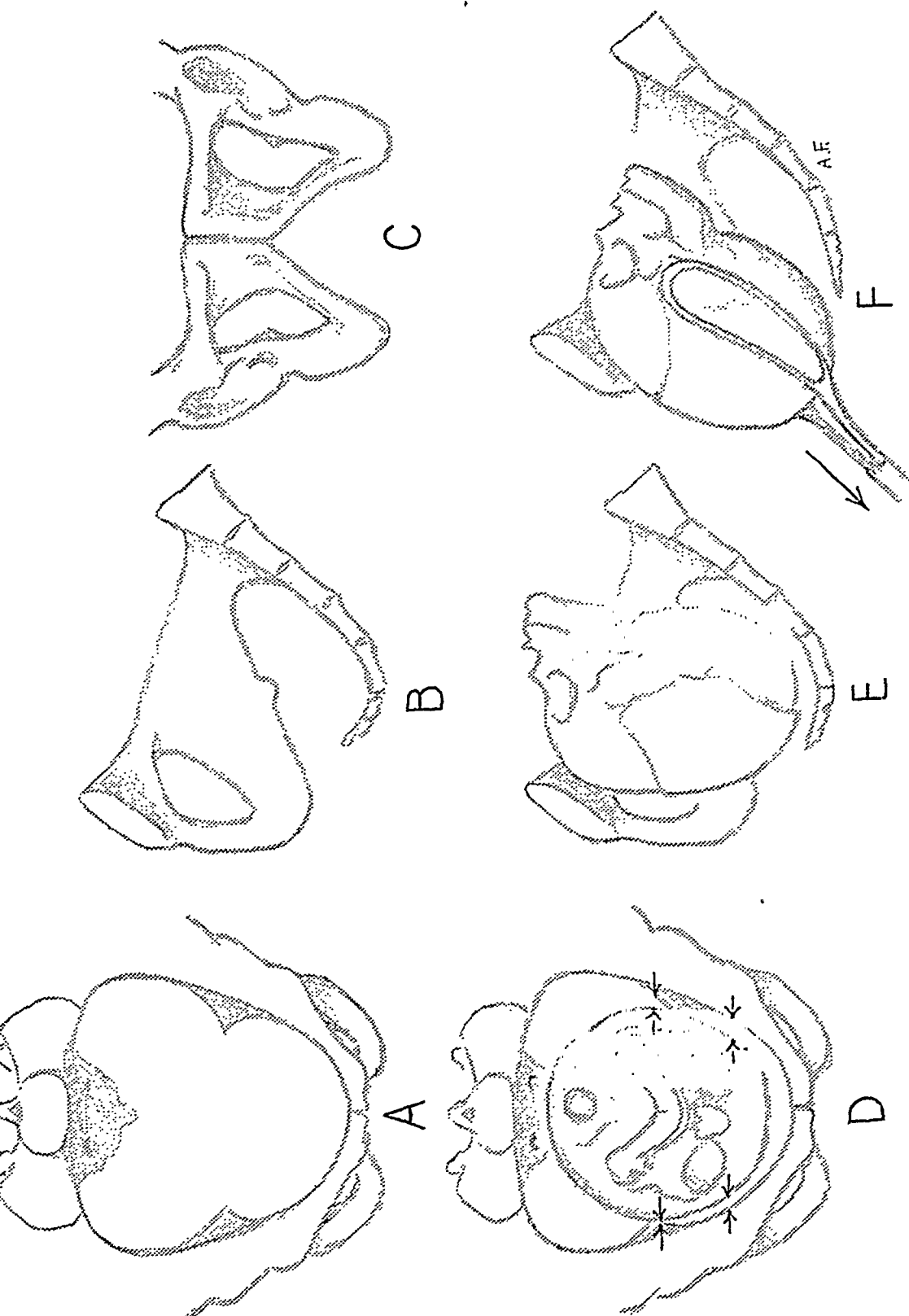


Fig. 10.—The mechanism for delivery from arrest in the occipitoposterior position to lower levels in the same position. A, Android-anthropoid type of pelvis with a long anteroposterior diameter, prominent ischial spines, and converging side walls. B, Lateral view to show ample posterior pelvic capacity because of an average curvature and inclination to the sacrum. C, Anteroposterior view of the slightly narrowed subpubic arch. D, Arrest in the occipitoposterior position, inlet view. E, Arrest in the occipitoposterior position, lateral view. F, A pelvic application of pelvic curved forceps is made and traction exerted downward and forward. A low complete rotation may be accomplished with caput in sight.

TABLE IX. DISTRIBUTION OF PELVIC TYPES ACCORDING TO THE MANEUVER USED IN THE DELIVERY IN MIDPELVIC ARREST IN THE OCCIPITOPOSTERIOR POSITION

(From 100 Cases of Midforceps Deliveries)

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	GYNECOID	ANDROID	ANDROID GYNECOID	PLATYPELLOID			NUMBER OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
Rotation to O.T. and descent to floor—low rotation	3	0	3	1	4	2	1	2	0	16
O.P. to floor—pelvic application	2	0	1	0	0	1	0	0	0	4
Face to pubis	1	0	0	0	0	0	0	0	0	1
Seanzoni at level of arrest	2	0	0	0	2	0	0	0	0	4
Manual rotation at level of arrest	0	0	0	1	0	0	0	1	0	2
Elevation with manual rotation	0	0	1	0	0	0	0	0	0	1
Spiral rotation with descent	0	0	0	0	2	0	0	0	0	2
Craniotomy	0	0	0	0	1	0	0	0	0	1
Total										31

vent anterior rotation. Descent to lower levels in the occipitoposterior position should not be attempted if the lower sacrum is forward. In one extreme anthropoid the child was delivered face to pubis.

Manual rotation at the level of arrest was successful in one case with a normal pelvis. Elevation of the head with rotation at a higher level was also employed on one occasion in an android-anthropoid type. Spiral rotation with descent was employed in two android types. Craniotomy through poor judgment was performed in one instance.

Thoms⁸ and others have drawn attention to the frequency of occurrence of the occipitoposterior position in the anthropoid pelvis. This observation, of course, is correct, but the anthropoid pelvis is an efficient pelvis, and there is usually spontaneous rotation or arrest in the occipitoposterior position at a low level with caput in sight. A study of Table IX indicates, however, that in medium forceps deliveries the arrested posterior position is found chiefly in android or in flat pelvis. The long oval shape is present at midpelvis to encourage this position by the presence of either converging side walls in the android type or a backward sacrum in the flat forms. This observation is important and stresses the value of a knowledge of pelvic shapes in the treatment of midpelvic arrest. In the low-midtype with arrest of the head in sight or on the pelvic floor, however, we find that the occipitoposterior position becomes once more characteristic of the anthropoid pelvis, as shown in Table X. Fifteen of the 22 cases showed extreme anthropoid tendencies with definite transverse narrowing throughout the pelvis. Descent of the head to the outlet usually implies good flexion and molding. Accordingly, anterior rotation is much more easily carried out than would occur if arrest took place at a higher level. Complete forceps rotation (Seanzoni maneuver) was performed six times at this low level of arrest, and in five instances the pelvis was anthropoid in shape. Elevation with manual rotation of the well-flexed and molded head was successful

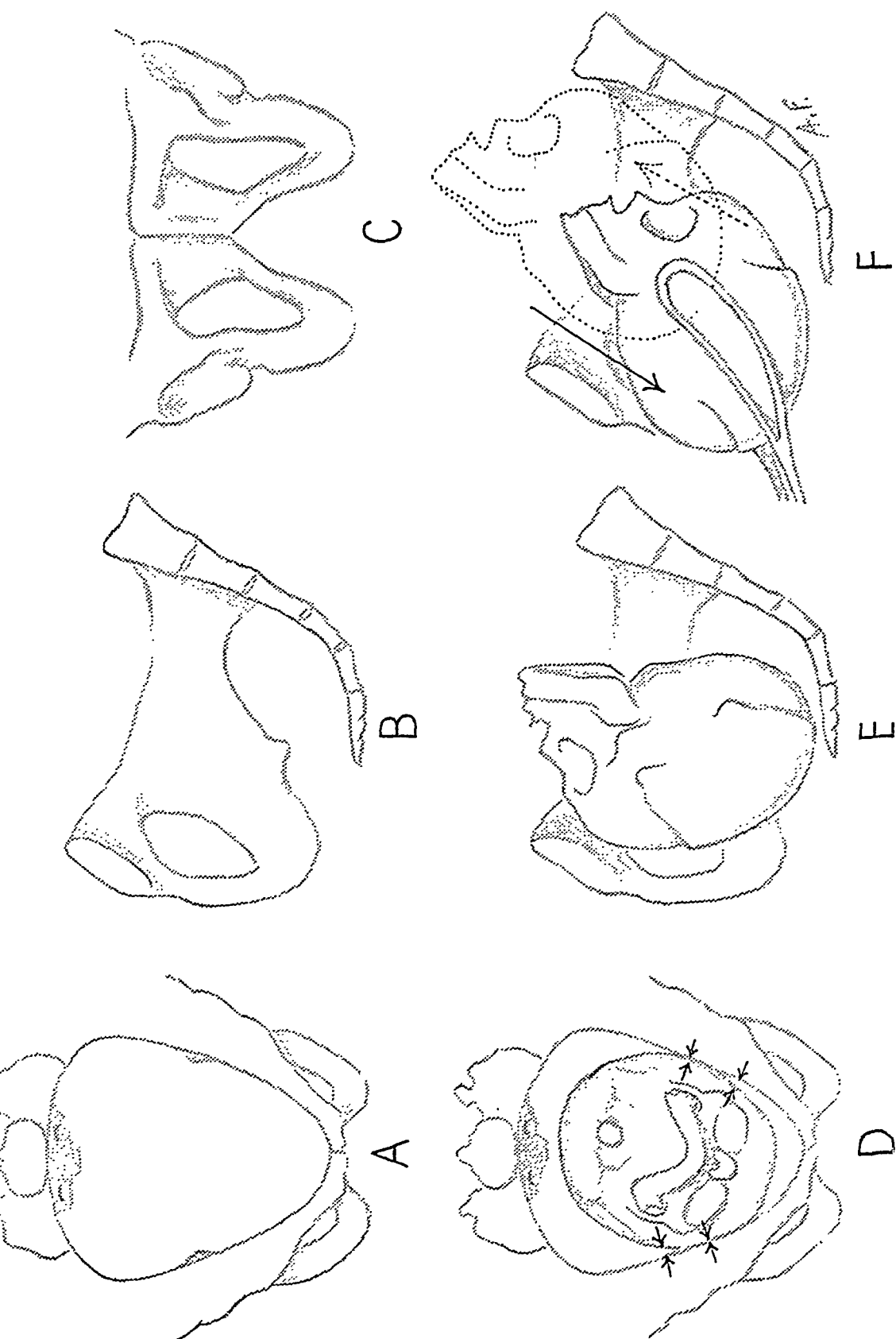


Fig. 11.—See opposite page for legend.

TABLE X. DISTRIBUTION OF PELVIC TYPES ACCORDING TO THE MANEUVER USED IN THE DELIVERY OF LOW MEDIUM ARREST IN THE OCCIPITOPOSTERIOR POSITION

(From 100 Cases of Low Midforceps)

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID ANTHROPOID	ANDROID GYNECOID	GYNECOID	ANDROID	PLATYPELLOID			NUMBER OF CASES
							GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
Complete Scanzoni	5	0	0	0	0	1	0	0	0	6
Complete manual anterior rotation	2	1	0	2	0	1	0	0	0	6
Manual to O.T. and Barton forceps	0	0	1	1	1	0	1	0	0	4
Face to pubis	0	0	1	0	0	0	0	0	0	1
Elevation with manual rotation	2	0	1	0	0	0	0	0	0	3
O.P. to lower levels low rotation	1	0	1	0	0	0	0	0	0	2
Total										22

three times in anthropoid types. The method used commonly in mid-pelvic arrest in the transverse position was used only four times in the twenty-two cases of the low-medium type, i.e., manual rotation to the transverse position with application of forceps, lateral flexion and descent with anterior rotation with caput well in sight. Face to pubis delivery with forceps was easily accomplished in one case with a marked android-anthropoid type with convergence.

One stillbirth resulted in an extreme anthropoid type after arrest occurred with caput in sight in the direct occipitoanterior position (Fig. 11). The baby was injured by repeated attempts at anterior rotation. The successful maneuver consisted in elevation of the head to the inlet with manual rotation. This particular patient has subsequently delivered an average-sized child face to pubis spontaneously. In several of these cases a forward sacrum resulted in fracture of the coccyx.

SUMMARY OF ANALYSIS OF ARREST IN THE OCCIPITOPOSTERIOR POSITION

Arrest of the head in midpelvis in the occipitoposterior position is most frequently associated with two pelvic types: the ample android type with slight convergence and the flat type with a backward sacrum. These latter two factors (convergence or backward sacrum) create ample anteroposterior space in the midpelvis to allow the occiput to rotate posteriorly. Incomplete flexion and molding of the head favor the maneuver of manual rotation of the head to the transverse position with the application of Barton forceps followed by lateral flexion and descent with low rotation. Arrest in more characteristic anthropoid forms has been successfully treated by a pelvic application of forceps to the occipitoposterior position with descent to a lower level and rotation with caput in sight. A Scanzoni maneuver was rarely used at the level of arrest and was successful only with a small child in an ample anthropoid form. In the low-medium arrest of the head in the occipitoposterior position the number of characteristic anthropoid forms in-

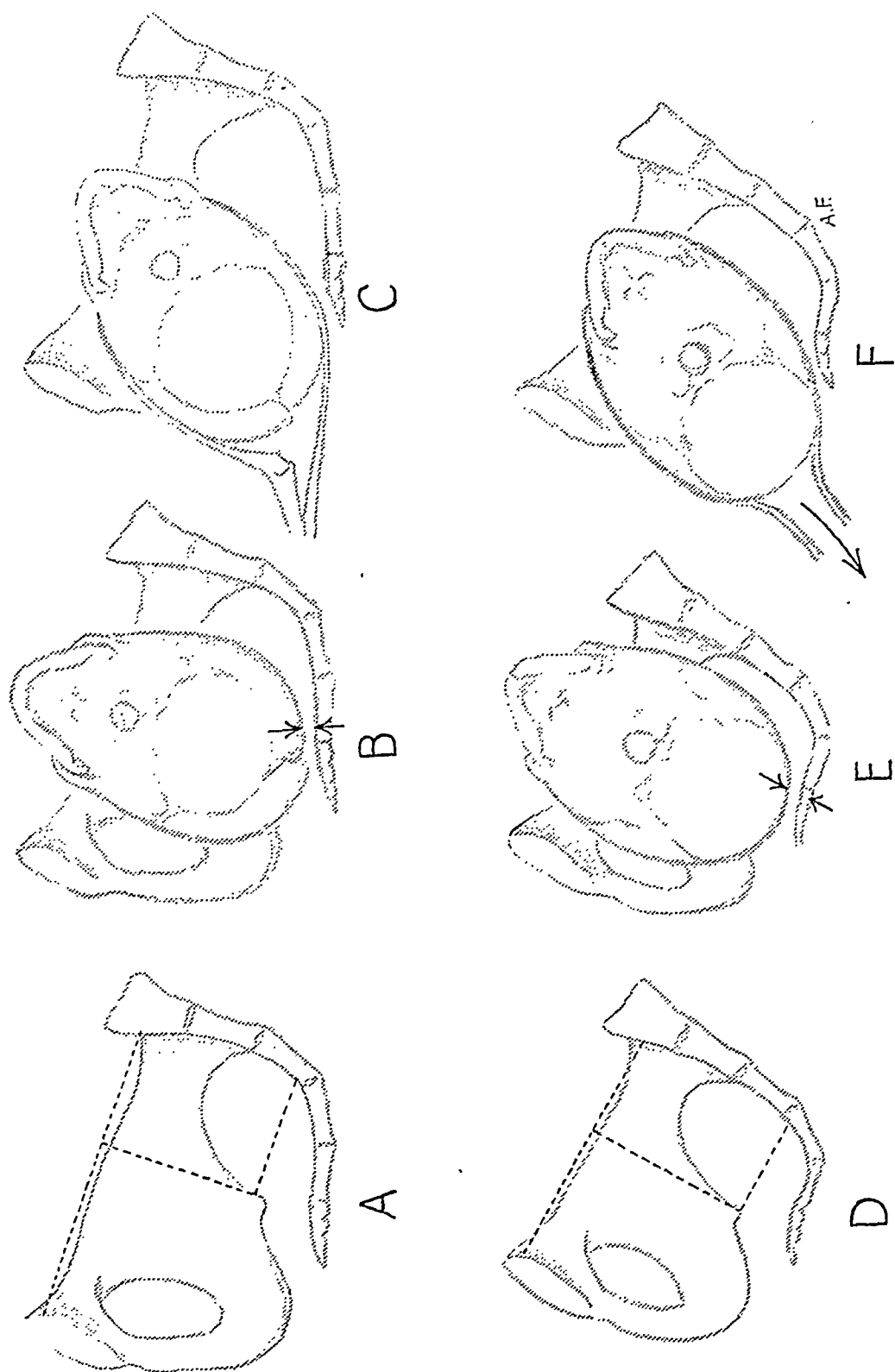


Fig. 12.—See opposite page for legend.

creases. Maximum flexion and molding of the head have allowed greater success in complete rotation by manual or instrumental methods than occurred with arrest at a higher level.

ARREST IN THE ANTERIOR POSITION

The type of pelvis associated with mid- and low-mid arrest in the anterior position is shown in Table XI. The first observation of interest is the absence of flat pelvis in the medium forceps group. This finding is in contrast to occipitoposterior midpelvic arrest in which the flat pelvis was occasionally noted in conjunction with a backward sacrum. The anterior position, however, as in the occipitoposterior arrest, is associated with two common architectural features, i.e., an ample anteroposterior diameter and converging side walls with a decrease in the interspinous diameter. The average interspinous diameter in these twenty-one cases was 10.4 cm.

With anterior arrests a cephalic application of forceps is easily made and the degree of traction necessary to effect delivery is, to a certain

TABLE XI. DISTRIBUTION OF PELVIC TYPES IN ARREST IN THE ANTERIOR POSITION FOR MID- AND LOW-MIDFORCEPS DELIVERIES

(From 100 Cases Each of Mid- and Low Midforceps)

	ANTHROPOID	ANTHROPOID GYNECOID	ANDROID	ANTHROPOID	ANDROID GYNECOID	GYNECOID	ANDROID	PLATYPELLOID			NUMBER OF CASES
								GYNECOID FLAT	ANDROID FLAT	TRUE FLAT	
Midpelvic arrest in the anterior position delivered by cephalic application of forceps	3	0	5	2	4	7	0	0	0	0	21
Low-mid arrests in the anterior position delivered by cephalic application of forceps	3	9	8	9	4	12	0	4	0	0	49

extent, dependent upon the degree of convergence of the side walls. The widest biparietal diameter of the head descends through the intertuberos diameter in front of the narrowed interspinous diameter.

THE PELVIC OUTLET AS INFLUENCED BY LOWER SACRAL VARIATIONS

Convergence of the side walls and variations in sacral curvature and inclination may effect a change in pelvic shape at and below the level of the ischial spines. The importance of convergence of the side walls

Fig. 11.—The mechanism of elevation with high manual rotation in extreme anthropoid types. *A*, Inlet view showing a long anteroposterior diameter with marked transverse narrowing throughout the pelvis. *B*, Lateral view indicating a slightly forward lower sacrum. *C*, Anteroposterior view of the narrow subpubic arch. *D*, Arrest in the occipitoposterior position in the lower fore pelvis with caput in sight. Attempts at anterior rotation at the level of arrest were unsuccessful because of the restriction in transverse diameters. These attempts at rotation seriously injured the child, causing a stillbirth. *E*, Lateral view of arrest in the occipitoposterior position. *F*, Delivery was finally accomplished easily by elevation of the head toward the inlet followed by manual anterior rotation at this high level. The head rapidly descended to the outlet where low forceps were applied.

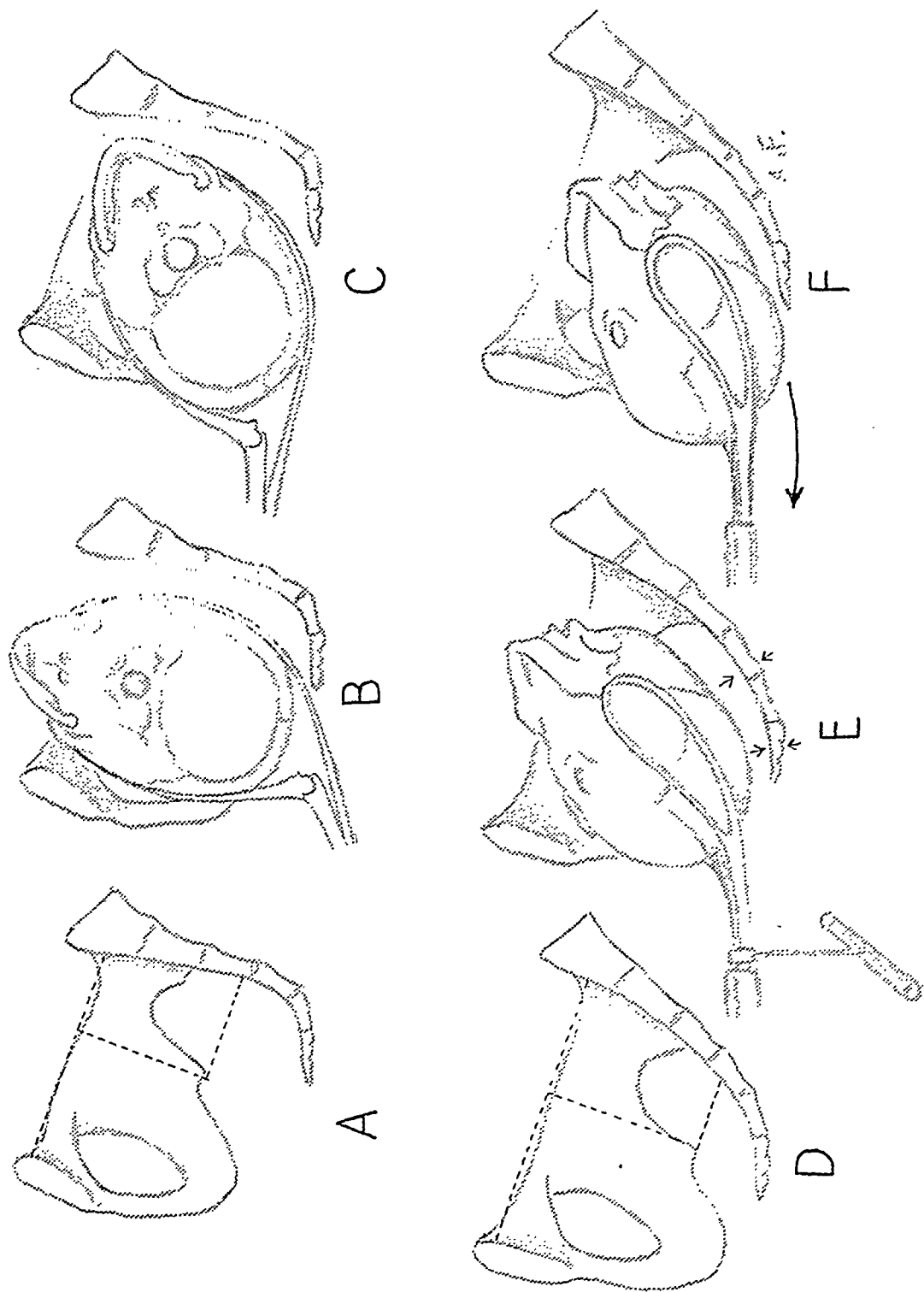


Fig. 13.—The significance of sacral variations. A, Lateral view of a flat android type of pelvis. The sacrum is straight with a slight backward inclination. The long posterior sagittal diameter at the level of the spines and the straight sacrum presented no obstruction to the descent of the head. Arrest occurred on the pelvic floor in the O.P.-O.T. position because the shape of the pelvis prevented anterior rotation. B, Lateral view of the arrest with Barton forceps applied. C, Lateral flexion with forceps removed the influence of the posterior pelvis and allowed low anterior rotation. D, Lateral view of an ample anthropoid type with a forward inclination to the sacrum. E, Arrest occurred just above the pelvic floor in the oblique anterior position because of the forward sacrum. Haig Ferguson forceps were applied. A downward and backward traction caused no advance of the head because traction force was misdirected against the lower sacrum. F, Elevation of the handles of the forceps caused slight extension of the head and with a downward and forward axis of traction, descent occurred easily.

has been repeatedly stressed in a discussion of the mechanism of forceps deliveries in the android and anthropoid types.

In the sagittal plane variations in the curvature and inclination of the sacrum affect the relationship of the lower sacrum and sacrococcygeal platform to the ischial spines and change the shape of the pelvic outlet. The frequency with which the forward sacrum was noted in the low-medium and medium forceps groups indicates the influence that restriction of posterior outlet space plays in pelvic arrest. An attempt has been made to illustrate the common types of lower sacral variation by the use of suitably chosen case studies.

In Fig. 12, *A*, *B*, and *C*, the lower sacrum curved forward to a considerable degree below the level of the ischial spines. The long posterior sagittal diameter at the level of the spines and the generally large pelvis allowed rapid descent until the head was arrested by the forward sacral tip. The shape of the outlet has been converted into a flat transverse oval which necessitates the delivery of the head to a lower level in the transverse position by forceps as illustrated.

In the example shown in Fig. 12, *D*, *E*, and *F*, a somewhat similar shape was formed at the outlet. The pelvis conforms to a large flat type which predisposes to a transverse arrest. The good sacral concavity and ample posterior sagittal diameter at the level of the spines allowed the head to descend to be arrested by the forward sacral tip. It was necessary to deliver the head in the transverse position through the fore pelvis until the biparietal diameter had passed the sacral tip before anterior rotation could be obtained. Barton forceps were used to flex laterally the head over the pelvic outlet close to the pubic rami. Barton forceps, however, failed to bring about descent because force, with traction, was misdirected against the pubic rami. After a cephalic application was obtained by pelvic curved forceps, the correct downward and forward axis of traction was determined, and the head descended in the direction indicated in the diagram (Fig. 12, *D*, *E*, and *F*).

The example shown in Fig. 13, *A*, *B*, and *C*, reveals the significance of increased posterior outlet space caused by a straight sacrum with a slightly backward inclination. The pelvis, a flat android, allowed the head to descend in the R.O.T.-R.O.P. position until the posterior aspects of the perineum began to bulge. The shape of the pelvis prevented rotation but the adequate posterior pelvic shape caused by the straight back-

Fig. 12.—*Significance of sacral variations.* *A*, Lateral view of a large anthropoid pelvis with a forward lower sacrum. The posterior sagittal diameter at the level of the spines is long. The sacrococcygeal platform is elevated toward the level of the spines. The sacral tip and coccyx extend forward under the spines causing a short anteroposterior diameter at the outlet and a flat outlet shape. *B*, Arrest of the head in the transverse position on the sacrococcygeal platform. The posterior parietal bone is depressed. *C*, Barton forceps were easily applied. The head was flexed laterally toward the outlet and anterior rotation was accomplished after the biparietal diameter had passed the sacral tip. *D*, Lateral view of an ample flat type of pelvis with good sacral concavity and forward lower sacral tip. *E*, Arrest of the large head occurred on the sacrococcygeal platform close to the sacrum. The good sacral concavity allowed descent to this level. *F*, Barton forceps brought the head close to the pubic rami by lateral flexion. With traction, force was misdirected against the symphysis. Barton forceps were removed and pelvic curved forceps were applied in cephalic application. The head easily descended by downward and forward traction. Anterior rotation occurred after the biparietal diameter of the head had passed the sacral tip.

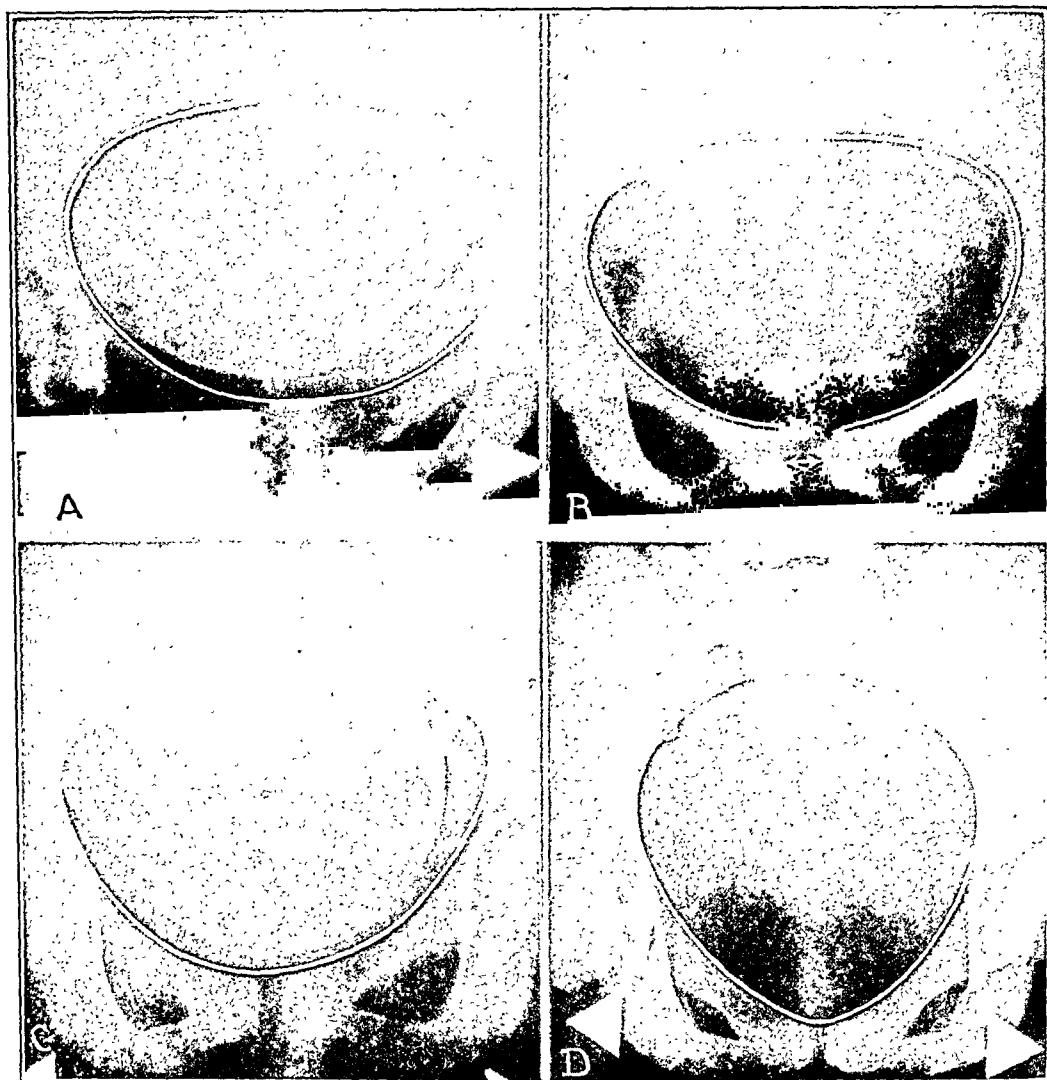


Fig. 14.—Pelvic type and mechanism of delivery in relation to stillbirth. A, X-ray No. 90557. Chart No. 309025. The pelvis conforms to the typical flat android type. Arrest occurred in midpelvis in the transverse position. The child was seriously injured by forceful attempts at anterior rotation with a poor cephalic application to the oblique anterior position. This type of pelvis favors the transverse mechanism described in Fig. 5. Weight of stillborn child, 3760 gm. The second child was delivered spontaneously, 4020 gm.

B, X-ray No. 89937. Chart No. 420649. (Case not included in the series of 500 cases.) The pelvis conforms to the true platypelloid type. Forceful attempts at anterior rotation of an arrested transverse position caused a separation of the symphysis and a stillbirth. The second child was delivered by cesarean section.

C, X-ray No. 164492. Chart No. 474972. The pelvis conforms to the typical android with practically straight side walls. Arrest of a large child occurred in midpelvis in the transverse position with the cervix fully dilated. Weight of child, 3856 gm. Forceful attempts were made to gain anterior rotation with pelvic curved forceps. The child died from intracranial hemorrhage twelve hours after delivery. This pelvis favors the transverse mechanism illustrated in Fig. 5.

D, X-ray No. 160792. Chart No. 300125. The pelvis conforms to the typical extreme anthropoid with straight side walls and a moderate subpubic arch. Arrest occurred in low midpelvis in the occipitoposterior position. Forceful attempts at anterior rotation were used. With difficulty the head was rotated to the transverse position and delivered to lower levels in this position with Barton forceps. This mechanism is obviously incorrect. The head should be elevated and rotated or brought to lower levels in the position of arrest. The child weighed 3610 gm, and was discharged living. It was badly shocked on delivery and suffered multiple fractures of the parietal bone.

ward sacrum allowed this low descent. The patient was delivered by low forceps. Barton forceps brought about anterior lateral flexion and anterior rotation was easily accomplished with caput in sight.

The influence of the forward sacral inclination is shown in Fig. 13, *D*, *E*, and *F*. The head was arrested in the direct anteroposterior position on the pelvic floor. Attempts at delivery with pelvic curved forceps failed when traction was exerted downward and backward. Force was misdirected against the forward sacrum. As soon as an attempt was made to extend the head, descent and an easy delivery occurred.

STILLBIRTH AND RELATIONSHIP TO THE MECHANISM OF DELIVERY

In the group of cases studied, there were 16 stillbirths. In a critical review of these cases we find that the mechanical procedures employed were open to criticism in at least 10 of them, since the correct methods of obtaining the optimum available space in the pelvis was not used. In 4 of the cases the amount of disproportion present at the time of the forceps operation was a definite contraindication to this procedure and either a cesarean section should have been done earlier in labor or, if possible, the labor should have been allowed to progress until further molding had occurred. In the remaining 2 cases, one infant died following a spontaneous delivery in which the shoulders became impacted, and another died in utero before any operative procedure was instituted. Of further interest is the fact that 5 of the women who had stillbirths subsequently delivered living children spontaneously. In 7 of the 16 cases the pelvis conformed to the extreme android form. In order to illustrate more clearly the importance of using good mechanics in delivery in an effort to avoid injury to the child and the maternal soft parts, the following 4 case studies have been chosen (Fig. 14). These 4 cases along with the example illustrated in Fig. 11 stress the following principles in mechanism:

1. Forceful attempts at anterior rotation in flat and certain android pelvic types should not be made or separation of the symphysis or stillbirth may result.
2. The transverse mechanism to lower levels should be encouraged in these forms.
3. Forceful attempts at anterior rotation in low occipitoposterior arrest in extreme anthropoid pelvis are equally dangerous.
4. The head should be elevated and rotated at a higher level or brought to a lower level in the occipitoposterior position.

During the last two years at the Sloane Hospital for Women, the attending staff have cooperated in the application of a knowledge of pelvic shape to the mechanism of labor. The incidence for cesarean section has not increased because of the better selection of cases for this method of delivery. The incidence of difficult forceps deliveries has decreased and there has been a definite decrease in the fetal mortality rate due, we believe, to the use of a better mechanism in forceps deliveries. The resident and interne staff, with instruction, readily grasp the principles of mechanism described in this report. Recently, in our clinic, there has been renewed interest in the roentgenologic study of the pelvis and fetal-pelvic relationships of patients in labor who are not progressing normally. Frequently, the recognition of a large head in a

These factors must be considered in the visual study of the fetal-pelvic relationships in the stereoscope. But when disproportion is noted in borderline cases, a trial of labor becomes the best means for determining the correct significance to place upon this supposed degree of disproportion.

Workers interested in methods of roentgen pelvimetry and cephalometry have attempted to use a measurable approach to the analysis of

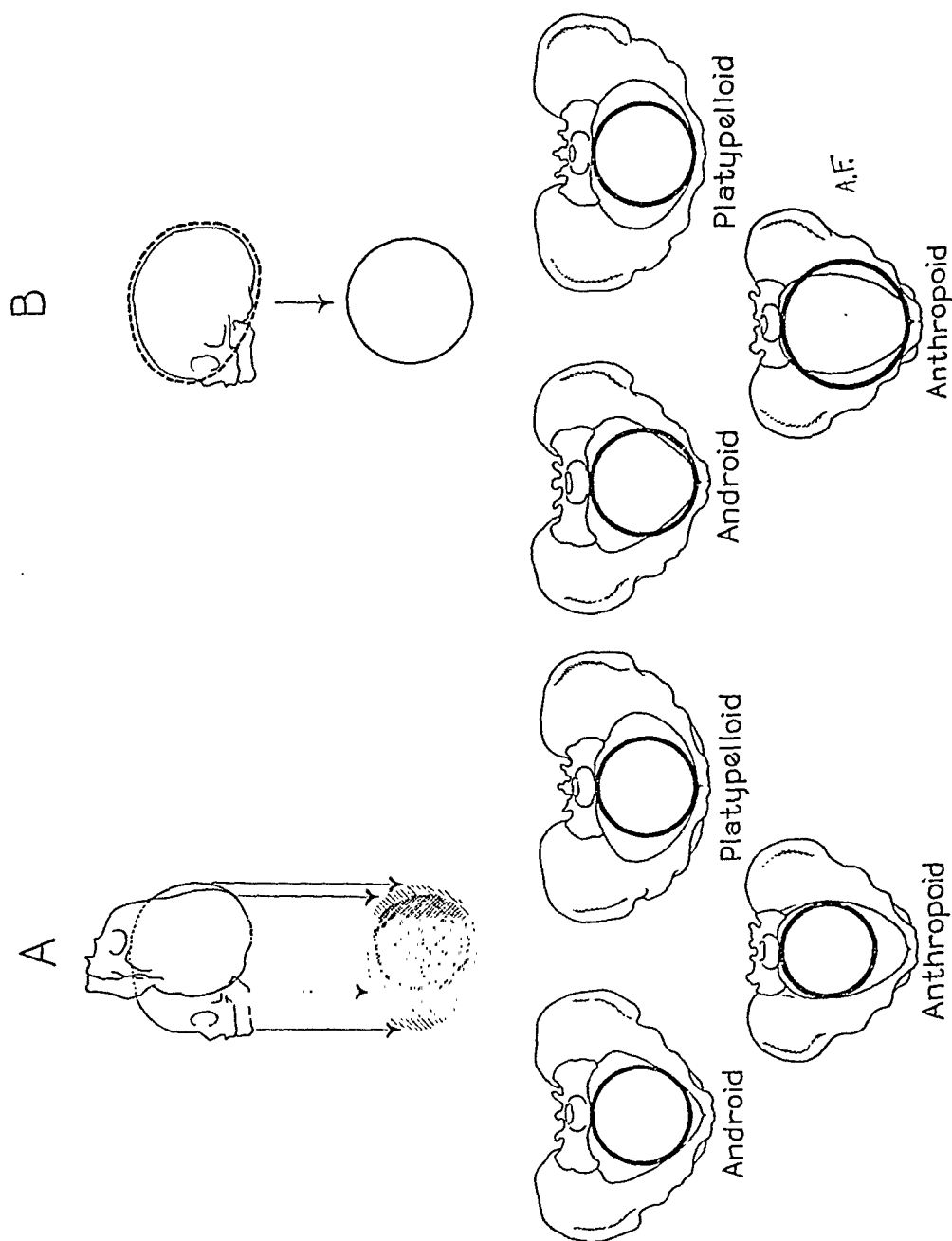


Fig. 15.—The comparison of head size to pelvic size. A, Authors' method. The surface area of the head presenting to the inlet varies from the circle of the biparietal diameter (smallest) to the silhouette of the occipitofrontal ovoid. The circle of the biparietal diameter may be compared to the circle inscribed within the pelvic inlet as obtained by use of the precision stereoscope. B, The method suggested by Ball and Marchbanks. The volume of the ovoid head is converted into a sphere which in turn is compared to the volume of a sphere the diameter of which equals the smallest pelvic diameter. Observe that a circle inscribed in the anteroposterior diameter in android and anthropoid types may not give the correct index of inlet size.

small pelvis has aided in the decision regarding the best method of delivery during the so-called trial of labor. If a forceps delivery later becomes necessary, the operator has an opportunity to attempt the mechanism he has interpreted as representing the optimum method for delivery from the study of the roentgenograms. As a result, greater conservatism in operative obstetrics has been practiced.

THE RECOGNITION OF DISPROPORTION

Disproportion between the head and the pelvis to even a major degree is occasionally observed in spontaneous deliveries, especially in multiparous women. The incidence increases in the low forceps, low-medium, and medium forceps, and cesarean section groups. The disproportion, in most instances, can be readily observed from the study of the stereo-roentgenograms in the precision stereoscope by visually attempting to compare the head and its biparietal diameter to the available space present at the inlet or in the lower pelvis. The observer, experienced in the use of the precision stereoscope, can actually measure one or more cardinal diameters of the fetal head besides noting the amount of clearance between the head and the pelvis. Flexion and molding of the head in labor decrease head size and represent such variable factors that, in practice, attempts to reduce the degree of existing disproportion to simple mathematical terms have not given satisfactory practical results.

But during this investigation which included many case studies obtained during labor, we have been interested in methods to estimate degrees of disproportion applicable to the precision stereoscope. The first problem deals with the index of pelvic size when the shape is abnormal. We have already shown that single pelvic diameters by themselves cannot be used to denote pelvic size in all instances (Table II to VI). In abnormal pelvises the size of the circle which may be inscribed within the pelvic inlet (under stereoscopic vision) represents a good index of pelvic size since the compensatory space existing around the circumference of the circle may be observed (Fig. 15A). Likewise, in many instances, the biparietal diameter of the fetal head can be measured directly or by the aid of graduated spherical disks fitted under stereoscopic vision into the approximate level of the biparietal diameter. If the circle which fits the biparietal diameter of the fetal head is compared to the size of the circle which fits the inlet, the degree of disproportion may be calculated. In examples of absolute disproportion between the head and the pelvis, the diameter of the circle of the inlet is usually larger than the circle of the biparietal diameter by 1 to 1.5 cm.

The surface area of the head presented to the pelvic inlet in labor is variable in size depending upon the existing degree of flexion and molding. The circle of the biparietal diameter represents its smallest size when the head shows extreme flexion. Since flexion is usually incomplete, the surface area presented to the inlet by the silhouette of the head is usually larger, reaching the maximum size in brow presentations.

occur in association with an adequate pelvis. The data presented show the importance of the bony pelvis but emphasize that there are other important factors to be considered in determining the ultimate outcome of labor.*

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DISCUSSION

DR. GERALD C. MELHADO, MONTREAL, CANADA.—Dr. Caldwell states that in a series of 130 midforceps operations in 69.3 per cent the pelvis was abnormal in size or shape, or both, whereas in our clinic (Victoria General Hospital, Montreal) during the past year in 111 midforceps operations definite abnormality existed in only 20 per cent. This situation is highly contradictory. It seems to me that there must be some explanation for the wide difference in the two clinics, more deeply fundamental than that explainable by methods of classification.

That arrest of the head in midpelvis is due to other factors than pelvic abnormality is generally recognized. In our clinic soft tissue dystocia, either with or without faulty attitudes and positions is a frequent cause for forceps interference. In fact, as already stated, the majority of operations were done on women who showed no definite contraction. Disproportion between head and pelvis is not necessarily due to or associated with pelvic abnormality.

Primary uterine inertia is a common cause of arrest and in our experience is most frequently associated with a posterior position of the occiput. An internal contraction ring situated about 8 to 10 cm. above the external os and around the child's neck frequently is found in such cases. In many instances it was the chief reason for the lack of progress.

I am entirely in agreement with Dr. Caldwell's statement that the occipitoposterior position should not be rotated at the level of arrest when such positions are associated with a typically transversely narrowed pelvis. His report on case studies 6 and 7 illustrates clearly this point, and in both instances manual rotation at a higher level would, in my opinion, have been successful and less likely to cause injury. That this is probably so was shown by the fact that in one of these cases in a subsequent delivery, spontaneous birth occurred from the L.O.A.

As a general statement, I am of the belief that if arrest of the head occurs in a given pelvis in the O.T. or O.P. position, rotation if considered advisable should be done at a different level and preferably free from pelvic control. Forceps rotation at the level of arrest accompanied by or with traction is dangerous, and is likely to result in severe injury.

In conclusion, there is a type of case of which no mention has been made, but which I understand will be considered in the published paper. This concerns the large head in the small pelvis considered by Dr. Caldwell as a slightly flat android type or in other classifications might be called generally contracted and somewhat flat. The possibilities for live births in this group depend upon many factors: efficient uterine force, moldability of the head, length of cervix, the presence or absence of a well-formed lower uterine segment and the type of sacrum. Uterine force and moldability of the head cannot be determined before labor. A short cervix and a well-formed lower uterine segment are favorable factors. A

*This investigation has been made possible through the cooperation extended by Dr. B. P. Watson and the attending and resident staff of the Sloane Hospital for Women and by Dr. Ross Golden and Dr. Paul C. Swenson of the Roentgen-Ray Department of Presbyterian Hospital. The authors take this opportunity to express their deep appreciation.

these borderline types. A unique method has recently been suggested by Ball and Marchbanks.⁷ The volume capacity of the fetal head is determined by the circumference measurements obtained from a single large lateral and a large anteroposterior film. The average circumference measurements are converted into a sphere, the volume capacity of which can be easily determined and recorded in cubic centimeters. It will be noted that conversion of the ovoid fetal head into a sphere enlarges the biparietal diameter for comparison to inlet diameters. The smallest inlet diameter and the interspinous diameter are chosen to associate with this spherical head volume by determining the volume capacity of the sphere with a diameter equal to either pelvic diameter. Ball has found that if head volume is 150 c.c. greater than the volume of the smallest inlet diameter the difference is too great to be safely handled by changes in head shape through molding, and a cesarean section is indicated. He has not as yet decided upon the limits of safety at the level of the ischial spines. This principle is illustrated in Fig. 15B.

By the use of the method proposed by Ball we have observed an easy delivery with a disproportion of 200 c.c. at the inlet. An easy low forceps delivery has occurred when over 300 c.c. disproportion was present between head volume and the volume of the interspinous diameter. These findings reveal the variable factors which occur in the mechanism of labor and show that, in most instances, it is not advisable to attempt to reduce the degree of disproportion to significant mathematical terms.

Accordingly, in a critical analysis of the merits of the method of volumetric head and pelvic comparison, several assumptions upon which the method is based are open to question. From the obstetric standpoint it is not advisable to convert a long oval object like the fetal head into a sphere for comparison with pelvic size. This conversion enlarges the biparietal diameter of the head above its existing size. Again, the smallest pelvic diameter is not always the proper index of pelvic size to use for comparison with head size to determine the existing degree of disproportion. The conversion of the volume of the ovoid head into a sphere places no significance upon head shape. Head shape has considerable practical significance. The question of disproportion in terms of ease or difficulty in labor remains unsolved except by clinical methods. Nevertheless, an optimistic view is justifiable and further study of a large series of cases by a modified volumetric approach and study of pelvic size when the pelvic shape is abnormal will eventually contribute accurate prognostic information.

To conclude this paper without calling attention to the fact that forceps are frequently used when the pelvis itself is adequate in size, might leave a false impression. In another study of 130 cases of midforceps operations, there were 40, or 30.7 per cent, in which the pelvis itself was ample as judged by our experience and by comparison with the types of pelvis seen in the spontaneous group. A discussion of these cases is beyond the scope of this presentation. It becomes evident, however, that a midforceps delivery cannot always be predicted on the basis of the pelvis alone. Roughly about one midforceps in three will

THE CESAREAN SCAR*

AN EXPERIMENTAL STUDY

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IN THE earlier editions of Williams' *Textbook* the statement is made in discussing the phrase "once a cesarean always a cesarean," that this is based in part upon the belief that the uterine incision heals by the formation of scar tissue, whence the term "cicatrix," and the newly formed connective tissue stretching and sometimes yielding when the uterus becomes distended. That such a belief is erroneous is shown in three ways. First, an inspection of the unopened uterus at the time of repeated section usually shows no trace of the former incision. If present, it appears as an almost invisible linear scar. Second, when the body of the uterus has been amputated, no scar is visible after hardening or at most a shallow vertical furrow is present upon the external and internal surfaces of the anterior wall, while between them no trace of the scar is apparent. Third, the most important histologic examination at the site of the incision shows that the uterus, just as all other organs containing smooth muscle, heals by a regeneration of muscle fibers and not by scar tissue.

Since it is well known that smooth muscle regenerates very slowly, and that in end-to-end intestinal anastomosis, the ends of the muscles are definitely separated by the intervening healing and are brought together eventually by the shrinking of the scar, Schwarz and Paddock felt this could also be demonstrated in the uterus experimentally.

In 1925, Schwarz and Paddock described the healing process in the early human uterus and clearly demonstrated the laying down of fibrin and fibroblasts along the line of incision in the early process of healing. These observations were followed by a series of experiments on the uteri of pregnant guinea pigs at term. This work conclusively showed that the process of healing was by scar tissue formation. In the early stages the marked development of fibroblasts could be seen along the line of incision, penetrating the cut muscle bundles very much like the limbs of a tree. As early as twelve days, in ordinary hematoxylin and eosin sections, it was difficult to demonstrate the line of incision, because of the intimate intermingling of cut muscle edge with fibroblastic proliferation.

In the sixth edition of Williams' *Textbook* the previously mentioned statements still appear, with the addition that enthusiastic advocates of the low cervical section contend that the rupture of the scar is less likely to follow than in the classical operation. They mention the work of Greenhill, who could demonstrate connective tissue in twenty-six instances out of thirty-one cases of low incision. They state that if this

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straight sacrum associated with this type of pelvis carries with it a greater degree of contraction in the pelvis than can be usually estimated. Reliance should be placed on experience and judgment. If disproportion at the brim is evident, the sacrum straight, and the head cannot be made to enter the pelvis fairly readily under anesthesia, it might be advisable to put this group in the elective cesarean class.

DR. BENJAMIN P. WATSON, NEW YORK, N. Y.—As I have followed the work of Dr. Caldwell and Dr. Moloy on the female pelvis I have become more and more convinced of its fundamental value. In the last two years they, along with Dr. D'Esopo, have been stressing the practical application of their findings. They have established the fact that pelvic configuration is largely responsible for the mechanism of labor in a particular case; that the mechanism can be predicted from a roentgenologic study of the pelvis; and that when delay in labor occurs the difficulty can be overcome in a rational way if one knows the type of pelvis, for then one may make use of its best available diameter. To arrive at this stage in their work they have had to spend much time in examining and interpreting many x-ray films taken before and during labor. Moloy's precision stereoscope is fulfilling all that was expected of it. One very quickly learns how to use it and having used it one is never satisfied to do without it in a difficult case.

The treatment of the occipitoposterior has been the subject of as much discussion as any other obstetric complication in our literature. From Scanzoni down to DeLee, Pomeroy, and Bill, different methods of handling this complication have been advocated. The present work of Dr. Caldwell and his associates would seem to indicate that while all of these various techniques have merit in selected cases, no single method is universally applicable to all cases. The midpelvis is much too variable in shape to make any single operative method the solution for all arrests of this sort. Of course, we all know that the well-trained obstetrician does not rigorously adhere to any one method but rather feels his way carefully as he goes along and by artfully modifying his favorite method is enabled to guide the head away from bony obstruction into the most available diameters. This, however, requires experience. Only after years of practice and perhaps many errors does the obstetrician acquire the so-called art of obstetrics which enables him to carry on in this way. Precise methods of evaluating the available space in the pelvis converts at least a part of this "art" into demonstrable and predictable facts which may be taught as such to the student of operative obstetrics. Granted then that the expert in most instances is able to carry out operative deliveries to the best advantage of both mother and baby without recourse to the refinements afforded by the x-ray, its value in teaching obstetrics cannot be overestimated.

DR. CALDWELL (closing).—I was rather surprised to find that in practically 70 per cent of our midpelvic arrests we found abnormality in the shape of the pelvis. The uterine contractions in these cases were weak and the labor pains inefficient, due to the shape of the pelvis, the lower uterine segment not permitting the presenting parts to fit squarely into the axis of the cervix. When this happens, it is not guided away against the anterior or posterior wall.

The majority of cases of stillbirth were due to so-called fetal distress. Personally I think it is a very great mistake to apply forceps hastily when the child is showing fetal distress and kill it by trauma. It is much better to put the presenting part up, relieve the uterine contraction if necessary, and then plan the operative delivery after the child has plenty of oxygen and the fetal heart is relieved. The woman may then continue the delivery herself.

in the high powered field, and as far as he is able to estimate, it is the only case on record where any question of regeneration of smooth muscle tissue is found in the human being. He was able to confirm the work of Loeb and Walsh as regards mitotic figures in the uteri of experimental animals.

The only experimental work on the uterine scar which we know of is that of Mason and Williams, which was done in 1910 on the uteri of guinea pigs. These observers did no histologic work, but merely tested the strength of the scar by

Fig.
1.



Fig.
2.



Fig. 1.—Human uterus, five days after cesarean section. Edges held together by a deposit of fibrin. No evidence of fibroblastic proliferation in this area.

Fig. 2.—Human uterus, five days after cesarean section. Marked proliferation of fibroblasts along the line of incision in the upper portion of the picture. Below is the smooth muscle of the uterine wall.

distending the uterine muscle, including the scar, with weights attached. As the weights were increased the strip ruptured and rupture always took place outside the line of incision. These experiments, seven in number, were carried out from seven to ten weeks after the operation.

Losee, in 1917, mentions the description of Couvelaire, and also describes his impression of early healing. He states that in the clear wound, after incision, leuco-

were the general rule it would not argue in favor of the operation as the connective tissue scar would be more liable to rupture than the muscular union which occurs after classical cesarean section. The same statements are made in the last edition of Williams' *Textbook*, published in 1937. Apparently the work of Schwarz and Paddock was overlooked as no mention of it was made under this discussion. The statement that there was scar tissue formation in the lower uterine segment and none in the upper incision seems somewhat illogical, because in both locations we are dealing with smooth muscle tissue of the same kind.

In view of these facts, we believed it might be of interest to review this subject as a whole and to present further experimental studies to emphasize these points. In 1906 the experimental work of Murphy clearly showed that so far as end-to-end intestinal anastomosis is concerned, healing takes place by scar tissue formation.

It is well known that in an end-to-end anastomosis a considerable exudate is formed along the line of suture which becomes organized as the result of marked proliferation of fibroblasts, which later contract and form an almost imperceptible scar between the muscle tissue. Descriptions and illustrations showing various stages of this process demonstrate that in the earlier stages there is marked separation of the muscle bundles, and as late as one month after, a definite linear scar, very thin, can still be made out between the edges of the muscle. These steps are particularly well illustrated in Gould's monograph on abdominal operations.

The other point concerns the regeneration of smooth muscle. It has been our opinion that smooth muscle regeneration takes place so slowly and meagerly that it could not bring about healing in so comparatively short a period of time. In our previous paper we reviewed the subject of smooth muscle regeneration and feel that it is important to include it again here.

McCallum, in his textbook on pathology, states that from experimental and other studies of the healing of defects in smooth muscle, there is very little activity in this region. Sometimes mitotic figures have been described and sometimes a new formation by amitotic division, but more recent studies tend to the idea that there is very little regeneration of muscle tissue in higher vertebrates, but that healing by scar tissue brings together the muscle edges at the site of defect. However, recent observations of Loeb and Walsh in a quantitative study on the regeneration in the uterus of epithelial, connective tissue and muscle tissue, show clearly that there is definite evidence of mitotic figures in the smooth muscle tissue as well as in the connective tissue, both after incision and compression by ligatures.

Loeb and Walsh conclude that mitosis in smooth muscle tissue is found between the fifth and eleventh days in the guinea pig, but only in specimens in which mitosis was also definitely present in the connective tissue. Also Loeb and Kuramitsu have shown that in the involution of the normal uterus in the guinea pig and rat, mitotic figures appear in smooth muscle layers during the first week of the puerperium, but are very rare after the first week.

As regards the regeneration of smooth muscle in the human uterus, the only evidence of such regeneration was described by Berry in 1922. Berry was able to demonstrate mitotic figures in the smooth muscle tissue of the uterus four days after perforation of the uterus by a curette. He found three mitotic figures on an average

RABBIT 1972.—Uterine scar after six days. In the uterus with the scar at six days, there is great progress in healing. Where the edges have been well approximated, there is very good union between the two sides. The endometrium everts to a variable degree to close the defect on the inner surface. The inner circular layer of muscle shows a change in the direction of the fibers with many fibroblasts

Fig.
3.



Fig.
4.

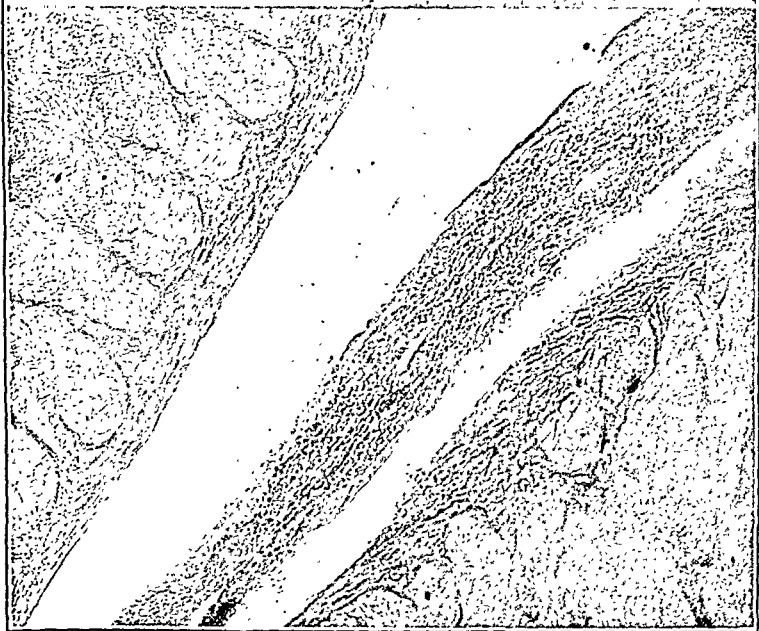


Fig. 3.—Rabbit uterus. Outer portion of three-day-old scar showing defect at peritoneal surface filled with fibrin and leucocytes. At the margins of the muscle there is the fibroblastic proliferation covering the muscle edges.

Fig. 4.—Rabbit uterus 1971. Three-day-old scar with Orcein-Van Gieson stain. Inner half of line of closure showing connective tissue proliferation covering each side of muscle edge and growing upward from endometrium.

between the ends of the muscle bundles. There is little change in the pattern of the outer longitudinal muscle layer. Beneath the peritoneal surface there is some connective tissue increase. In sections where the approximation was not so good, there

cytes, red blood cells, fibrin and later, young connective tissue cells separate the surfaces. These afterward are obliterated and eventually the muscle and fibrous tissue strands, separating the bundles, assume the relationship normally observed in other areas of the post-partum uterus. Other than a thickened peritoneum there is no scar tissue observed microscopically or macroscopically in the line of former incision when examined at subsequent cesarean section operation, provided healing has occurred under normal conditions. Losee's descriptions are chiefly those of the late scar at subsequent cesarean section. Although he mentions this description of early healing, apparently it is not based on studies of early wounds.

We are including several of the illustrations of our previous paper in this one, to make comparisons with our findings in the rabbit. The accompanying legends for these illustrations, we believe, are sufficient to describe the findings.

The material for this study was derived from the uteri of rabbits. Abdominal section was done on pregnant rabbits. The uteri of these rabbits were opened. Each fetus and its placenta were removed and the uterine wall closed by silk sutures. In most cases it was necessary to make two or more incisions to empty the uterus. Healing was allowed to progress for various periods of time, three, six, nine, twelve, eighteen, and twenty-six days. At the end of the desired number of days, the animals were sacrificed and sections were obtained at the site of the uterine scar.

While these observations were being made, three human uteri were obtained that contained scars of previous cesarean sections. In the human uteri the scars were all more than two years old and were obtained at the time of subsequent cesarean section and hysterectomy.

In each case the sections were stained with hematoxylin and eosin to show the usual tissue picture and with Orcein-Van Gieson stain to show differential histology. With Orcein-Van Gieson stain the muscle fibers stain yellow, the connective tissue red and red-brown, while the elastic tissue, as seen in the blood vessels, stains almost black. The fibroblasts stain almost a pure light red.

RABBIT 1971.—Uterine scar after three days. In the three-day scar a very marked and rapid reaction has taken place. In spite of the very recent incision of the wall, the repair process is well advanced. Due to the quite recent damage to the wall, the sections were quite fragile when cut. Repeated sections cut from celloidin and paraffin blocks show the main changes to be as follows:

The defect is clearly seen in all sections. Over the "V" shaped defect at the peritoneal surface is an accumulation of fibrin, old blood and leucocytic reaction. This tends to form also about the free ends of the suture material. Beneath this debris there is a new growth of fibroblasts growing from the connective tissue at the peritoneal surface. As the defect is followed it is seen that the tissue at the edge is composed of fibroblasts that run in the direction of the incision. The muscle layers have retracted in such a way that the outer longitudinal layer turns inward, while the inner circular layer of muscle fibers has entirely pulled away from the region of the defect.

The endometrial layer in general at the vicinity of the wound shows a tendency toward eversion. The endometrium shows fibroblastic activity in the stroma in the region of the wound. The stroma shows a fresh fibrillar appearance taking on increased pink stain in the Orcein-Van Gieson stained sections.

area covering the defect. There is a separation of the two sides of the muscularis with the intervening portion entirely filled with a fairly dense connective tissue. In this, several new blood vessels and a few small endometrial glands are seen. The direction of the stroma of this tissue is parallel with the direction of the incision. At the ends of the muscle bundles on either side is an area composed of fine fibroblasts from the connective tissue of the muscle. At the inner ends of these fibers, they tend to direct their course toward the central connective tissue. At the endometrial layer there is some thickening and extension toward the muscularis.

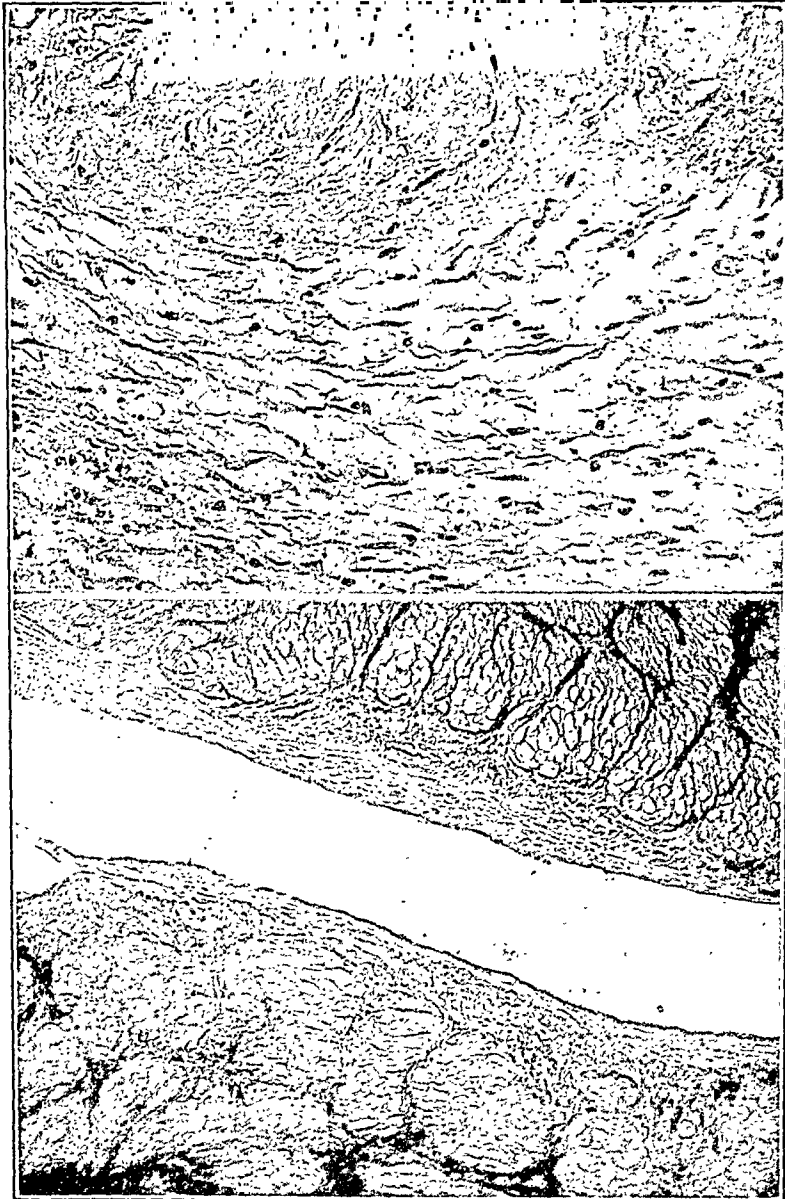


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Fig.
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Fig. 7.—Rabbit uterus, twelve-day-old scar. High power through central healed portion stained with hematoxylin-eosin stain to show fibroblasts forming line of closure.

Fig. 8.—Rabbit uterus 1971. Three-day scar, showing arrangement of connective tissue along the ununited edges of the incision and about the muscle bundles. Orcein-Van Gieson stain.

RABBIT 1962.—Uterine scar after ten days in control rabbit. In the unsutured scar the union has been unusually good. The area of union is found only with difficulty. There is very little reaction on the peritoneal surface. In the endometrial layer there is some increased thickening toward the muscularis. There is slight re-

is much the same reaction in the tissues, but the edges have separated and the fibroblasts run in the direction of the line of incision and cover the muscle edges. The epithelium from the peritoneal surface and from the endometrial surface grows over the defective portion of the surface.

RABBIT 1964.—Uterine scar after nine days. In one of the scars there is the formation of a fistula with the endometrium everting for a distance and the peritoneal surface inverting, with epithelial lining to the entire tract. Over the "V"

Fig.
5.



Fig.
6.



Fig. 5.—Rabbit uterus 1972. Section through entire thickness of uterine wall at six days. Healing has been retarded in this scar. Note connective tissue covering edges along entire thickness of wall.

Fig. 6.—Same as Fig. 5, with Orcein-Van Gieson stain.

shaped defect at the peritoneal surface there is a marked fibrin and leucocytic reaction. At the edges of the area is a fine fibroblastic proliferation. The appearance is that of a formation of a fistulous tract with a protective reaction over the defective portion.

The better healed scars at nine days show the following uniform changes. At the peritoneal surface is a fine fibroblastic reaction with thickening over the entire

loose network which dips in at the site of closure, and becomes thinner and more dense until it is lost in the connective tissue among the bundles of the longitudinal muscle layer. There is little change in the circular layer except for some reduction in the thickness due to eversion of the endometrial layer.

In one of the twelve-day-old scars, union between the two sides has failed to take place and a fistula has resulted in part of the length of the scar. This fistula is lined by epithelium from endometrium to peritoneum. There is no reduction in thickness of the uterine wall at this region. There is an increase in loose connective tissue beneath the epithelium and covering the muscle layer along the sides of the fistula. The circular muscle has been reduced at the site of the fistula. The longitudinal layer is not much altered.

RABBIT.—Uterine scar after twenty-six days. Under low magnification the transverse section of the uterus showed that the wall, at the site of the closure, was not appreciably different in thickness in any of the sections. With low magnification there was some paleness in the area of closure.

About the silk sutures there was considerable reaction with increase in connective tissue and some giant cell reaction. In these areas the pattern of the tissues seemed considerably disturbed. The tissue fibers about the sutures assumed a more concentric arrangement.

When the circular layer is seen, it is almost impossible to follow the course of union, due to the course of the connective tissue which is in general parallel to the direction of the muscle fibers. In the Orcein-Van Gieson stains no definite line of union could be seen in the circular layer.

CESAREAN SCAR 17991.—The sections of the uterine wall at the site of the scar show no evidence of thinning of the entire wall. The course of the scar is traced through the entire section with difficulty, due to the variation in the course of the line of union. On the peritoneal surface there is some irregularity and increase in connective tissue beneath the peritoneum. This moderate increase of loosely arranged connective tissue is seen dipping into the muscle of the outer third of the uterine wall at the site of union.

In the middle third of the uterine wall the continuity of the scar is lost, due to the ramification of the connective tissue (which is only slightly increased) between the muscle bundles.

In the inner third of the uterine wall the connective tissue again shows some increase along the line of closure. Here the course of the muscle fibers becomes a little more parallel to the line of union. In this more evident portion of connective tissue are areas of decidual cells which become increased in numbers as the decidual surface is approached. This eventually becomes part of the decidual layer itself. Decidual cells in considerable numbers are found in one section in the line of union as far out as the outer half of the uterine wall.

CESAREAN SCAR 17779.—In each of the blocks from the four levels of the uterus in which the scar was seen in the gross, portions of the scar may be seen microscopically. The scar is represented only by a line of union between the muscle bundles. There is no evident thinning of the uterine wall.

Starting at the peritoneal surface the site of the scar is evidenced by a slight depression at the surface. Here the peritoneal surface is irregular. By following the muscles across the section it is possible to follow the course of the line of union of the two sides of the old incision. This union is by no means a straight line, but it follows a very irregular course. The course runs down between the muscle bundles with numerous ramifications. It is traced by the irregularity in the pattern of the muscle bundles on either side of the site of incision. As these bundles approach the site of incision, they frequently change their course or become loosely interlaced across the area that was the original defect. Marking the original break in the uterine wall, which has now firmly united, is the slight increase in connective tissue present between and about the muscle fibers that at first marked the edge of the incision. This rather loosely arranged connective tissue forms a reticular structure about the muscle bundles at the site of the defect. In no place is there any wide area of connective tissue between the muscle bundle ends. This may be traced by following the pattern in the Orcein-Van Gieson stained sections.

duction in the thickness of the circular layer toward the outside, due to the retraction of fibers in the inside portion of the circular layer. Very little increase in connective tissue appears in any of these sections. Good union occurred in each scar.

Fig.
9.

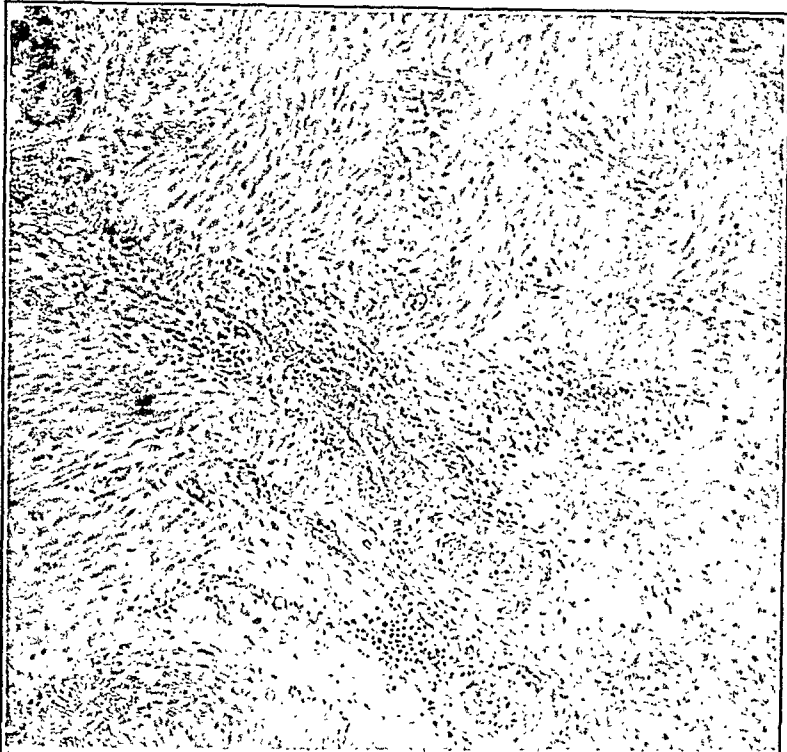


Fig.
10.

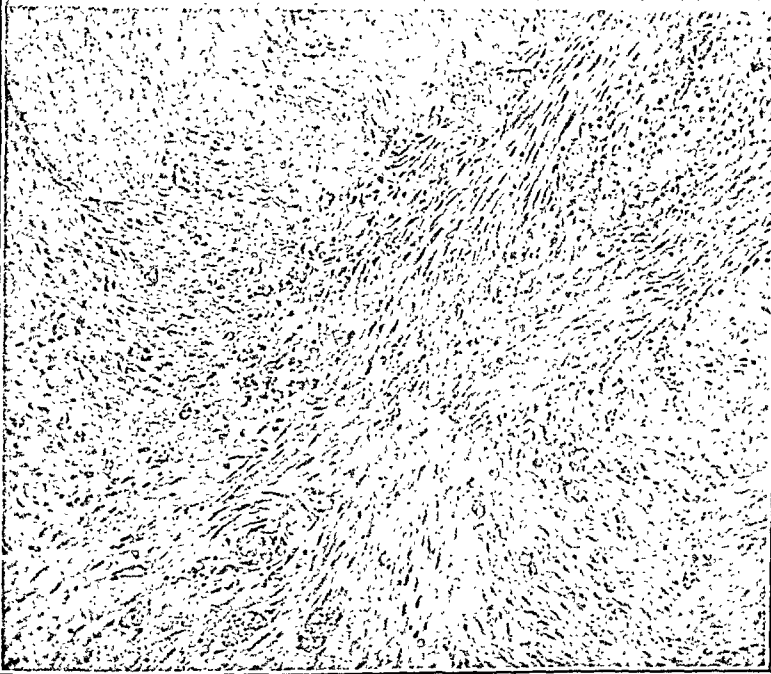


Fig. 9.—Rabbit uterus 1972. Section through portion of well healed scar at six days. Note defect in muscle pattern closed by connective tissue proliferation.

Fig. 10.—Rabbit uterus 1964. Nine-day scar showing closure of incision by connective tissue.

RABBIT 1955.—Uterine scar after twelve days. In all of the scars of this age there is more reaction about the peritoneal surface than in the older scars. This reaction is characterized by an increase in the subperitoneal connective tissue, arranged in a

In addition to the study in the rabbit, one pregnant dog was used. The animal was sacrificed on the fifth day and the incision shows beautifully the extensive fibroblastic proliferation on each side.

CONCLUSIONS

From the study of the series of uteri from pregnant rabbits, we feel that the healing process is entirely similar to that in guinea pigs, that healing takes place chiefly by the proliferation of fibroblasts along the line of incision entering the spaces between the adjacent muscle bundles. As the scar shrinks, this becomes less perceptible, and it is difficult to demonstrate the line of incision with ordinary hemotoxylin-eosin stains after a two-weeks' period. Special stains, namely Van Gieson, bring out this differentiation.

In our previous paper, we clearly demonstrated the process of early healing, similar to that found by Losee. In uteri removed after previous cesarean section, the scar is frequently imperceptible, but in many instances increased connective tissue can be demonstrated. The reason that the scar is imperceptible is due to the marked shrinking of the newly developed connective tissue and the fact that it branches off in between the muscle bundles along the line of incision. Also, if the suturing has been well done, the muscle edges are in close apposition, which necessitates only a comparatively narrow line of healing. As this shrinking takes place, the normal relationship of smooth muscle and connective tissue, as occurs in the normal pattern of the noninjured uterus, is similar.

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DISCUSSION

DR. LYLE G. McNEILE, LOS ANGELES, CALIF. (By Invitation.)—Notwithstanding the fact that during the nearly twenty years which have elapsed since the authors first reported their conclusion that healing in the recently incised uterus occurs by scar tissue formation and not by muscle regeneration, no acceptable evidence to contradict their conclusions has been published. We still find the unqualified statement in textbooks published as late as 1937, that there is no scar tissue formation in such wounds. In these most recent textbooks the discussant had been unable to find any reference to the authors' earlier works on the subject.

The studies of Dr. Schwarz may be of great help in the problem of repeated cesarean section. On this subject we find violent differences of opinion. A large group of obstetricians maintain that the dictum "once a cesarean always a cesarean" should govern our procedure in every case which has been subjected to abdominal hysterotomy, regardless of the indication for the first cesarean section.

Another group considers this an exaggeration, explaining that "This . . . is in part based upon the belief that the uterine incision heals by the formation of scar tissue and that the newly formed connective tissue stretches when the uterus becomes

As the decidual surface is approached, we find the loose connective tissue replaced by decidual tissue which has developed at the portion of the line of closure. These decidual transplants may be found in some of the sections to a much greater depth than in others.

Fig.
11.

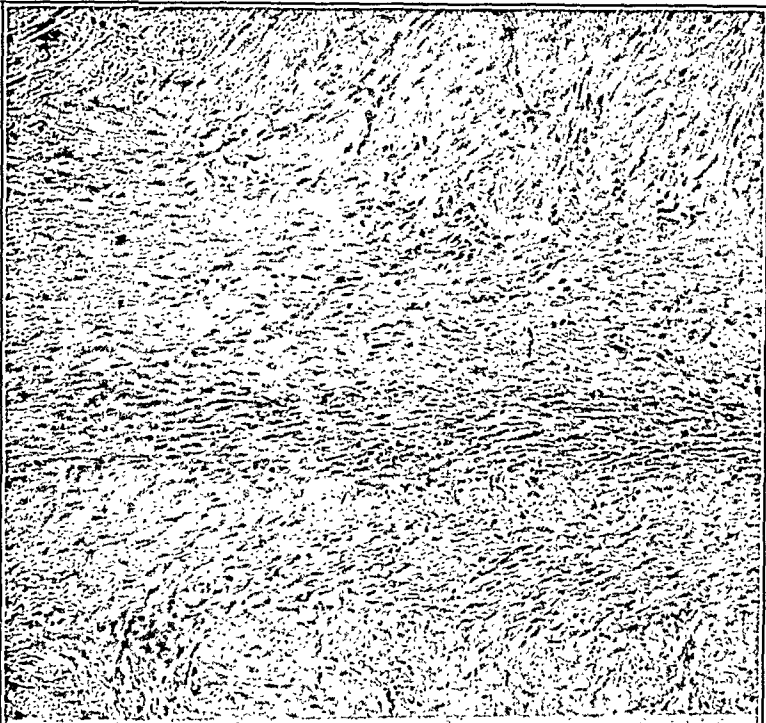


Fig.
12.



Fig. 11.—Dog uterus, five-day scar. Hematoxylin-eosin stain. Section showing the thick line of fibroblasts holding the edges of the incision together.

Fig. 12.—Dog uterus, five-day scar. Orcein-Van Gieson stain of Fig. 11. Heavy black structure indicates a large amount of fibrous tissue along the line of incision.

Where the decidual tissue extends deeply out into the muscle there is also marked invasion of the tissues by trophoblastic cells.

formation, and the decreased vascularity, with the fact of the incision being away from the site where the chorionic elements might enter into it, explains the more satisfactory healing.

Occasionally when resection of the tube is done for sterilization purposes, a regeneration may occur with complete functional restoration. The situation is somewhat similar in the uterus. If one can get a satisfactory closure, it seems to me one should get similarly a complete restoration in the uterine body, which after all is nothing but a tube. It would therefore seem that there must be other extraneous factors to explain the weak closure when it occurs.

Finally, in one part of the sections shown, a fibrous tissue skeleton was drawn across the wound. May I ask Dr. Schwarz whether he thinks that later perhaps the muscle would grow over and lead to a more natural appearance?

DR. FRED L. ADAIR, CHICAGO, ILL.—I am showing a section from the uterus of a woman, forty-nine years of age, who was operated upon for multiple fibroids of the uterus. She had had a classical cesarean section in her one and only pregnancy in 1921, and her uterus was removed in October, 1937.

In this scar there is a definite predominance of the scar tissue, which is shown by the blue stain, over the muscular tissue. This should answer the question as to the predominance of the scar tissue in the uterine incision.

DR. SCHWARZ (closing).—Answering Dr. Fraser's question, whether muscle regeneration could play any considerable part in later making the cesarean scar imperceptible, I would say that if muscle regeneration took place to any considerable degree in these scars it would be an additional factor, but I do not believe it would bring about any immediate healing. I believe the scar shrinks to such a degree that it simulates the normal pattern. Muscle regeneration is so slight and so small in amount that, in my opinion, it cannot play any considerable part in the healing of any incision.

distended." This group firmly believes that healing is entirely by the process of muscle regeneration. It is obvious that if the authors' work is accepted, there must be some modification of this attitude.

A third group professes to be able to evaluate the integrity of the uterine scar by scrutinizing the history of the postoperative period following cesarean section. They claim that thinning of the uterine wall, or weak scar, is always associated with a febrile puerperium following the earlier operation. Except in the presence of marked disproportion, they do not consider the repetition necessary if the puerperium has been afebrile.

As a matter of fact, it has been repeatedly shown that an afebrile convalescence is not a criterion of the strength or weakness of a cesarean scar. Many of us have often observed, during an elective cesarean section performed before the onset of labor in patients whose previous convalescence has been entirely normal, the phenomenon of the so-called "window scar" formed by the complete separation of the old incision, with the infant clearly visible through the membranes.

No accurate statistics to show the incidence of rupture of the uterus through the scar of a cesarean section performed according to recent technique, are available at the present time. The old statistics show an incidence of about 4 per cent, but they are based upon a series of sections performed many years ago. I believe that at the Los Angeles County General Hospital the incidence is somewhat higher than this. In a statistical study of uterine ruptures occurring in my clinic, I found that our maternal mortality due to uterine rupture following previous cesarean section was 20 per cent. This compared very favorably with our mortality of 90 per cent due to ruptures in which a previous section was not a factor. The late Asa B. Davis, in a report covering ruptured uteri at the New York Lying-in Hospital, had similar results, and in explaining them he made one pertinent observation concerning the clinical effect of scar tissue formation in cesarean scars. He said, "The more favorable prognosis may be the result of the healed tissue in and about the previous cesarean scar, since this tissue does not bleed so freely as the tissue about a traumatic rupture." He evidently had reference to scar tissue formation.

DR. JOHN R. FRASER, MONTREAL, CANADA.—Ever since Säger first described the technique of cesarean section, the history of the operation has been a recital of a series of efforts to find the most suitable point of entrance into the uterus. We have two more or less accepted methods, either an incision through the fundus, a mesially placed incision, or a low segment incision. It is very difficult to contrast the incision in these two sites because anatomically they vary so greatly in structure. If one studies the uterus of a pregnant woman after the fifth month, visualizing the circulation by injection, one finds that the arterial supply of the fundus is tremendously increased and that the transverse vessels have now become very much larger. The fundus is completely encircled by these vessels, whereas in the lower segment there is practically an avascular zone. Now an incision through the fundus severs this ring of vessels. It is also difficult to provide the same environment for the healing of the fundal wound as in the lower segment, because of the restlessness of the fundus.

We believe, in addition, that the histology of the lower segment is different from the histology of the fundus, in that there is relatively little change in the lower segment as compared with the uterine body itself in pregnancy. There are thus many factors that will enter into the complete and perfect closure above when compared with the lower segment.

In surveying our cases at the Royal Victoria Hospital of 123 repeat sections, it was found that in eleven instances the wound in the uterus was decidedly unsatisfactory. It was interesting to inquire into the history of some of these patients. I discovered that practically none of these 11 patients had had a satisfactory convalescence free from tissue morbidity or general infection. Therefore, it seems that infection must play a considerable rôle in the prevention of a perfect closure in the fundus, whereas, in the lower segment the lessened tendency to hematoma

death, of treatment, or of classification. Each representative reports verbally the case from his own institution and gives such additional data as are requested in discussion. Ten or twelve such stillbirths are considered each month, the remainder being analyzed by the smaller original committee. Naturally at the monthly meetings the discussion leads off into numerous channels; many questions of policy and of recommendation come up for consideration. For all of us the vision of responsibility and of field of duty is enlarging as the investigation progresses.

For purposes of uniformity and of comparison, the standards of the Children's Bureau and the Subcommittee on Stillbirths of the American Public Health Association have been adopted. Although the law in Pennsylvania calls for the reporting of births as early as fourteen weeks,

THE OBSTETRICAL SOCIETY OF PHILADELPHIA

STUDY OF STILLBIRTHS (STILLBIRTHS OF 20 OR MORE WEEKS GESTATION)

1. Place of Birth _____ Delivery at _____ M. _____ 19____
(Name of hospital, or street address if home delivery) (House) (Mews) (Flat) (Year)

2. Mother: Name _____ Marital Status _____ Age _____ Race _____ Private Charity _____
(State and Birth) (Color and Race) (Class)

Previous Medical History: _____

History of Endocrinopathy: _____

3. Children of this Mother:
(As the case of this birth)
(and immediate this birth)

RESUME OF PREVIOUS PREGNANCIES						
NO.	YEAR	ABORTION PREMATURITY FULL TERM	METHOD OF DELIVERY	DATE OF CHILD	IF DEAD CAUSE	REMARKS
1						
2						
3						
4						
5						
6						
7						
8						
9						

4. Present Pregnancy:
Was pregnancy normal? _____

Specify complications: _____

Was serologic test for syphilis taken? _____ Date Result _____ Treatment for syphilis _____

5. Labor: Duration { 1st stage _____ 2nd stage _____ Complications: _____

Was labor induced? _____ Indications: _____ Method: _____

OVER

Fig. 1.—Card for reporting of stillbirths, front view.

we are including in this study only those in which the pregnancy is of twenty weeks or more duration. We follow the definition of stillbirth suggested in the Rules of Statistical Practice of the Public Health Association:

“A stillborn child is one which shows no evidence of life after complete birth (no breathing, no action of heart, no movement of voluntary muscle). Birth is considered complete when the child is altogether (head, trunk, and limbs) outside the body of the mother, even if the cord is uncut and the placenta still attached.”

The card used for the collection of data (Figs. 1 and 2) is similar to the one used by the Children's Bureau, in that it contains all the items of data which are included in the latter. To these, however, have been added a number of items which we felt would prove of interest and importance: previous medical history, history of endocrinopathy, more

PROBLEMS IN THE ETIOLOGY AND PREVENTION OF STILLBIRTHS*

THADDEUS L. MONTGOMERY, M.D., PHILADELPHIA, PA.

MY REMARKS are based upon preliminary observations in a study of intrauterine fetal death which is being conducted by the Obstetrical Society of Philadelphia. The appointment of a special committee for this purpose was made in the spring of 1937, the plans and organization for study were completed during the summer, and the collection of data begun in the fall. The assignment is for a year's investigation. While that period is incomplete, my intention here is to present an outline of the organization and a résumé of such problems in causation, classification, and prevention as may be of interest to a national organization which has for one of its purposes improvement of obstetric practice.

The subject of fetal mortality has not, in this country at least, received the same degree of attention as have considerations of maternal death. This is perhaps a natural tendency, for the exigency of maternal death was, and still is, great. A number of reports of fetal mortality have emanated from individual institutions^{1, 2, 6, 8, 9, 16-18} but only recently have studies of city, state, and national scope been undertaken. The investigation by the Children's Bureau of the Department of Labor^{4, 11, 15} of a cross section of hospitals of the United States has awakened new interest in the stillbirth problem. The analysis conducted by Bundesen, Fishbein, Dahms, and Potter in Chicago³ has proved stimulating. Valuable data were contributed by Plass and Alvis¹⁰ in a survey of problems in Iowa. Reports of interest have come from Wisconsin⁷ and Ohio.¹² Each community has approached the question in an individual way.

Philadelphia has attacked this problem in characteristic fashion. Being, as ever, short on funds but long on cooperation, the collection of data is being performed by unpaid voluntary representatives of each hospital, a plan of organization similar to that which was worked out for the Maternal Welfare Committee of Philadelphia by Dr. Philip F. Williams, whose pioneer work and suggestions have paved the way for this study. The selection of younger men from each hospital has been encouraged in order to spread the educational advantage of the study over as large a number as possible.

Once a month this larger committee of hospital representatives meets and analyzes a number of the reports which have been submitted during the previous four weeks. Inasmuch as it is impossible to bring all of the stillbirths before this larger group, cases are selected for consideration in which there is question of circumstance, of diagnosis, of cause of

*Read at the Sixty-Third Annual Meeting of the American Gynecological Society, Asheville, N. C., May 30 to June 1, 1938.

by attending physicians. Some forty or fifty of the remaining hospital reports as well as a number of the home reports would not normally be expected in until some time after this report was started. Of the hospital stillbirths more than 90 per cent are being reported by our hospital representatives and by the time the study is completed we hope to have them all. Of the home deliveries about 60 per cent are being reported by attending physicians.

We have not attempted to push the investigation of home cases beyond the mere request for information and the providing of cards for report. It has not seemed worth while or feasible to go further. For the sake of completeness it was decided originally to include the home deliveries in the study, fully realizing that the significance of the data thus obtained might be limited. Our expectations in this direction have proved correct, for only in the case of obvious etiologic factor has it been possible to ascribe a cause for fetal death. In most cases, lacking the assistance of autopsy report and clinical studies, the conclusion "Cause Unknown" has had to be set down.

As the study progresses we find the causes of death in the hospital cases falling into well-known groups:

Toxemia and nephritis in the mother	12.0%
Antenatal syphilis	9.0%
Complicated labor with birth injury	16.0%
Monstrosity and congenital deformity	7.0%
Placenta previa and premature separation	
of the placenta	12.5%
Prolapse of the cord	5.0%
Placental infarction	4.0%
Coroner's cases with no data available	3.5%
Miscellaneous conditions	16.0%
Cause unknown	19.0%

In many instances it has proved no simple task to fix a primary cause of death. In order to elicit as many factors as possible we provided space at the end of the card for the reporter's opinion as to the factors residing in the mother, the fetus, and the secundines, and recognizable factors in the father. The result is that a number and a variety of conditions have been reported, some of which were simply concomitant circumstances (such as cord around the neck); other important etiologic factors, e.g., toxemia in the mother, or infarction of the placenta; and many which were terminal pathologic lesions in the fetus, e.g., asphyxia, atelectasis, intracranial hemorrhage, exsanguination. Whether to set down the terminal lesion in the fetus as the primary cause of death, or the pathologic state of pregnancy or labor, was often a subject of debate.

Sellers¹³ in an excellent exposition of this problem, strongly favors the terminology suggested by the League of Nations Committee and the nomenclature employed by Holland. These terminologies emphasize the primacy of the pathologic factors in pregnancy and labor. Much may be said for them inasmuch as they lay the finger of accusation upon conditions which we hope by improved obstetric practice to prevent. Accordingly the primary cause of death in placenta previa would be set down as placenta previa and not as asphyxia (though the latter might be mentioned as a concomitant lesion), the cause of death in birth injury would be disproportion or malpresentation, or contracted pelvis and not intracranial hemorrhage (although it too might be mentioned as a terminal factor).

The Children's Bureau is approaching this problem with an open mind. The principal object of its study is to derive a satisfactory nomenclature for the causes of stillbirth. In our Philadelphia analysis we have as yet adopted no very definite policy and shall probably have to go back over all of our cases and make recapitulation of the causes of death.

detailed résumé of previous pregnancies, nature of prenatal care, autopsy findings, special examinations of placenta and cord, and puerperal progress of mother. In this we were apparently justified, for without adding much to the burden of the reporter we are accumulating data which will add considerably to our knowledge when a final analysis is made.

Cards sufficient in number for the reporting of a year's stillbirths were placed in the hands of each hospital representative, together with directions for filling and return stamped envelopes for the mailing of each month's reports. For the reporting of stillbirths which occur in the home, a report card, directions, and return stamped envelope are mailed to the physician who attended the case. Every effort has thus been made to eliminate mechanical difficulty in getting reports in.

6. Was there an operation for delivery?.....Specify:.....		<small>(Include: Low, mid and high forceps; version and extractions; breech delivery; caesarean; craniotomy, etc.)</small>	
Indications for operation:.....			
7. Drugs and anesthetics given:.....		<small>(In first and second stage, exclude third)</small>	
8. When did fetal death occur?		Was fetus macerated?.....	
Before labor.....	Before operation.....	When did Fetal Heart Sounds cease?.....	
During labor.....	During operation.....	Remarks:.....	
9. Fetus: Sex.....	Period of Gestation.....Weeks	Length.....Weight.....	If plural birth, Number in order of birth.....
		<small>(Crown to heel)</small>	
10. Autopsy?.....Findings:.....			
11. Placenta and cord:..... <small>(Normal or abnormal. Specify lesions)</small>			
12. Puerperal condition of mother:..... <small>(Cause of mortality or morbidity if they have occurred)</small>			
13. Causes of the stillbirth (Indicate which is considered primary):			
(a) Found in the Fetus:.....			
(b) Found in the Secondines:.....			
(c) Diseases and conditions in mother during pregnancy and labor:.....			
14. Remarks:.....			
Record prepared by.....		Date.....	

Fig. 2.—Card for reporting of stillbirths, back view.

The Department of Public Health under Dr. William C. Hunsicker has manifested enthusiastic interest and has given admirable cooperation. Copies of stillbirth report, birth certificate, and death certificate are forwarded to us as soon as the original is received at City Hall. Notification is then mailed to the hospital representative, informing him of each of the stillbirths in his institution. Without this information and assistance the committee would be at a loss to carry on.

PROGRESS OF THE ANALYSIS

From Oct. 1, 1937, to April 30, 1938, 449 certificates of stillbirths were forwarded to us by the Department of Vital Statistics. Of these, 361 occurred in the hospital and 88 in the home. At the time of last summation 290 of the hospital cases had been reported by the hospital representatives, and 45 of the stillbirths in the home

In several instances reported it was obvious that the obstetrician had weighed the ultimate safety of the mother against the precarious state of the fetus, the labor having reached an advanced stage, and decided that the fetus should bear the burden of risk. Such cases were classified as nonpreventable fetal deaths.

In contrast with these few exceptions, there were 32 deaths in which faulty judgment or faulty technic on the part of the physician placed responsibility for unfavorable outcome at his door. Such cases have to do with bad obstetrics, and bad obstetrics has to do with maternal values as well as fetal, particularly in the misapplication of intrapartum tactics of delivery. Bad as the situation appears it is certainly not as bad as it was a number of years ago. My grounds for this statement is the parallelism in decline of maternal and stillbirth rates in our city (Fig. 3). In Fig. 3 it is to be noted that as the puerperal death rate has improved, there has been a steady fall in the stillbirth rate. Other phases of obstetric practice have to do with this improvement, but the more judicious application of operations of delivery has played an important rôle.

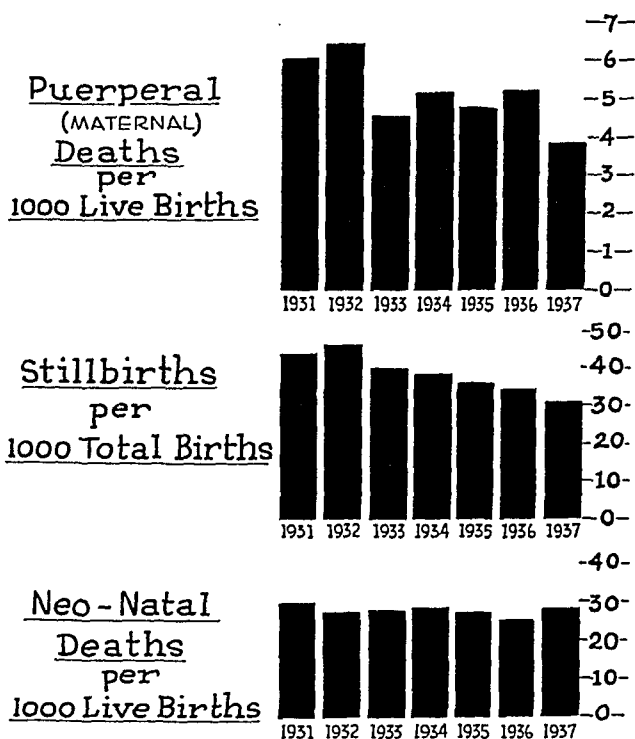


Fig. 3.—Maternal and fetal mortality (Philadelphia, 1931 to 1937).

Two years ago, in response to the suggestion of the Maternal Welfare Committee of the County Medical Society, a policy of consultation in all cases of delayed or difficult labor was adopted by the hospitals of Philadelphia. The analysis of stillbirths is affording a splendid opportunity to watch how it is being carried out and what its benefits are to be. Ultimately such policy must redound to benefit of mother and baby.

TOXEMIA AND NEPHRITIS

Toxemia of pregnancy and chronic nephritis complicating pregnancy stand close to birth injury as a cause of fetal fatality. At present little can be said for the preventability of fetal death in these cases; in the vast majority of cases we found that the fetus had succumbed to the disease or had been sacrificed before viability, in the interests of the mother. A few instances were held to be preventable in which prenatal care had been neglected or refused by the patient, or where supervision had been mismanaged by the physician. Considering the obscure nature of the toxemias,

CONSIDERATIONS OF PREVENTION

The interest of the committee in Philadelphia is not alone in the causes of death and the classification of factors, but also in the problem of preventability. For this reason each case is approached with the thought in mind, How might this fetal death at another time be prevented? With such considerations uppermost we have found ourselves, as we look back over our cases, dealing with three groups of fetal death: first, those in which the cause of death is obscure and unrecognizable and the possibility of prevention therefore nil; second, those in which the cause of stillbirth is evident but in which the possibility of prevention is limited by the inadequacy of our present knowledge; and third, those in which the cause of stillbirth is known, the method of prevention is known, but for one or more reasons the available knowledge has not been applied. Of the latter group there are many and antenatal syphilis is a striking example.

ANTENATAL SYPHILIS

The time is ripe for constructive action to prevent the further occurrence of antenatal syphilis. The laity has been made familiar with the problem, the physician is conscious of the requirements of the situation, now all that is required to remove this disgraceful blot upon obstetric practice is united and cooperative action.

Because of these considerations a subcommittee upon antenatal syphilis has been appointed to make further study in Philadelphia of this single problem. They report that of 24 stillbirths from antenatal syphilis, 20 were possibly preventable, that of 49 cases of unknown cause of death, 15 had no maternal Wassermann, that the practice of obtaining serologic tests in private patients is not a universal one, that while serologic tests are taken upon charity patients in hospital service, frequently the registration is late and the diagnosis and inception of treatment are still later, that pregnant patients are loath to go to several different clinics for observation and treatment during the burdensome period of pregnancy, and therefore are prone to neglect their ante-partum treatment, that unless measures are found for the inauguration of effective treatment before the fifth month of pregnancy, there is no certainty of prevention of congenital syphilis in the newborn infant.

We are now seeking authorization for cooperative action with the pathologists and the syphilologists to amend these difficulties: To reduce the expense of Wassermann rate to semiprivate patients, to subtly propagandize the necessity for serologic tests in all pregnant women, to set standards for syphilitic treatment in pregnancy, and provide detailed plans for the organization of antisymphilitic clinics as an integral part of the obstetric department, or at least as a branch service of the general antisymphilitic department of the hospital.

Such endeavors are rapidly becoming of themselves a separate undertaking in the maternal and fetal welfare of our city. When they are successfully consummated, we will feel that the science of obstetrics has made one of its proper contributions to the field of preventive medicine.

BIRTH INJURY

The importance of birth injury as a preventable factor in fetal mortality is well recognized. In our statistics to date, 16 per cent of the stillbirths have been attributed to birth trauma; of these three-fourths were held to be preventable.

Diagnosis of injury was made upon clinical history, circumstances of delivery, and revelations of autopsy. Since autopsies were not performed in a number of the cases, it is evident that a good deal was left to the opinion of the reporter and the judgment of the committee.

From the standpoint of fetal safety alone all deaths from birth injury might be classed as preventable, inasmuch as for each labor some extreme form of delivery might have been chosen to insure the intactness of fetal structure. From the broader standpoint of practical obstetrics, such criteria are not, however, acceptable. The committee has taken the latter viewpoint in its consideration of birth injuries.

coming more common acquisitions of the attendant at labor. Methods of prevention and treatment which are now in more or less experimental stage will merit wide acceptance and practical application. Further studies in the embryology and biologic processes of the developing ovum, and better understanding of the balance of hormonal secretions will pave the way for a solution of problems which now seem hopelessly obscure.

In the meantime, more and more attention is being paid to the cooperative study of fetal and maternal mortality. Physicians are analyzing the bad results in obstetric practice and pointing out for themselves the paths which lead to improvement. Such procedures can only have a salutary effect.

Those of us who participate in the Philadelphia study are encouraged to feel that the purposes for which it was undertaken are being accomplished, that data of interest and of value are being accumulated, that attention is being directed to an important problem; and we are trustful that as a result of this cooperative enterprise obstetric practice will be further improved.

Acknowledgment is made to the hospital representatives, to the clerical force, and to the other members of the original committee, Dr. Arthur First and Dr. John F. Sharkey.

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1930 CHESTNUT STREET

DISCUSSION

DR. FRED L. ADAIR, CHICAGO, ILL.—There are three major problems so far as mortality is concerned which have confronted the obstetrician. One, of course, is maternal mortality, another is fetal mortality, and a third is neonatal mortality. These problems have challenged the obstetricians because the rates in the past have remained unchanged for many years. A further problem arises due to the fact that studies of these mortalities indicate that many of the deaths are preventable.

Just what constitutes a stillbirth is a little difficult to define statistically. According to the rules of reportability in this country, at least in many states, any fetus which shows any sign of life whatsoever has to be considered a live birth. This rule applies in most of the registration areas to births after the fifth month of gestation. If one figures the fifth month as the calendar month, it amounts to from twenty-one to twenty-two weeks, so that any infant that is born after the fifth month, if it does not show any signs of life, would be regarded as a stillbirth. The period of previability extends from this time until the twenty-sixth or twenty-eighth

this phase of obstetric pathology presents a dark picture for the life of the fetus in utero. Our knowledge of the subject up to the present has permitted us to extend but little hope in moderate and severe cases.^{9, 17}

Recent favorable reports upon the effect of active preparations of vitamin E¹⁴ in pregnancy toxemia, and in vasculonephritic disease have extended some hope in an otherwise black situation.

ANTENATAL HEMORRHAGE

Antenatal hemorrhage, the result of placenta previa, and premature separation take a heavy toll. In the former, considerations of maternal welfare make it often necessary to sacrifice the nonviable pregnancy in order to arrest hemorrhage. In the latter, the frequent association with nephritis and toxemia makes separation an ever present hazard, and the nonpreventable nature of the toxemia defies the best efforts of the obstetrician to salvage fetal life.

Even so, our figures for fetal mortality are better than those of years ago, for prompt diagnosis and prompt interference, by abdominal hysterotomy when feasible, have saved many babies.

Shute maintains that the early symptoms of premature separation, or at least of hemorrhagic infarction, can be recognized clinically, and that if heavy doses of wheat germ oil are instituted, further extension of the process can often be arrested. On this question we are open to conviction; our own observation has been that abruption of the placenta can be more certainly prevented if wheat germ oil therapy is instituted early in pregnancy in all patients who present a history of previous placental disturbance.

Prompt diagnosis and prompt institution of surgery insure, in most cases of placenta previa, a living child if the latter has reached the period of viability. The value of the x-ray in aiding with this diagnosis is not fully appreciated. The opaque medium technic by which the space intervening between bladder and presenting part has been held as a criterion of the presence of low implantation has not proved useful.

OTHER CAUSES OF FETAL DEATH

There are other causes of fetal death in which the outlook for improvement is discouraging: prolapse of the cord, knots, torsion, and constriction; necrosis of the placenta; congenital deformities and monstrosities of the fetus; peculiar disturbance associated with endocrinopathy in the parent. In this connection a number of cases have come up before the committee for discussion, in which possible hypothyroidism and extreme obesity have been associated with fetal death. In none of these instances have the studies of metabolism and endocrine function been sufficiently extensive to point certainly to the etiologic factor in fetal fatality. In addition there are those cases in which clinical history, details of labor, and autopsy fail to shed any light upon the cause, either in full-term or premature fetuses.

For the solution of these latter difficulties, we must wait upon a further progression in our general scientific knowledge. In the meantime, we urge upon our hospital representatives the careful study of all available data, the gross and histologic study of placenta, membranes, and cord, and in the institutions where facilities permit, such studies of endocrine function and hormone titre as may throw light upon these numerous questions. In those cases, particularly, in which there is a history of previous stillbirth, meticulous studies must be conducted during the course of pregnancy.

PROSPECTS FOR IMPROVEMENT IN STILLBIRTH RATES

Notwithstanding these difficult problems in management and occult factors in etiology, I can visualize a steady reduction in stillbirth rates in the next decade. Those qualities of insight, judgment, and technical ability which make for low mortality in skillful private practice are be-

a greater percentage than the hemorrhages. Toxemia is associated with ablatio placentae in a small group. Cord complications account for about 2 per cent, medical disorders in the mother for about 4 per cent, and syphilis for 1 per cent or less in the neonatal group.

In the stillbirth group these hemorrhagic conditions of the mother make up a very large group in which they were considered to be the cause of the stillbirth, and a relatively small group where some other conditions seemed to be the cause. The toxemia with ablatio placentae, cord prolapse, medical complications and syphilis played small parts also. Syphilis with us does not play as great a role as in some other sections, perhaps due partly to the fact that we do not deal with so many colored patients in whom the incidence of syphilis is universally higher than among the whites.

Studies of this kind, with autopsies showing as accurately as possible the causes of death, will help us in evaluating the proper obstetric procedure to prevent some of the deaths of the fetus and the newborn infant.

DR. GEORGE W. KOSMAK, NEW YORK, N. Y.—Mortality statistics from gross death rates have proved unsatisfactory. It was not until detailed studies based on individual case records were developed in the New York Academy of Medicine and the Philadelphia County Medical Society, that adequate estimates became available of the preventability factors in pregnancy fatalities. This same type of investigation must be applied to our stillbirths and neonatal deaths if we are to obtain any definite knowledge of how to prevent them, and it is of interest therefore to note the work of Dr. Montgomery and his Committee in Philadelphia.

The importance of reducing fetal deaths should be of paramount importance in aiding to maintain population balance in this country which is being affected both by voluntary and involuntary birth restriction. Although there is still a comparatively small excess of births over deaths, this does not furnish a conclusive and reliable indication of the capacity for future natural growth of our population, as pointed out by Dublin and others. This is because the birth rate and the death rate are both affected by the age distribution which is manifesting a shift to the older groups. If American reproductivity is admittedly on the decline, compensation must be sought and this can be accomplished by doing away with, as much as possible, the wastage of fetal life. Abortions in this country have been estimated by Taussig to number over 600,000 annually and the U. S. Census Bureau claims that 78,000 stillbirths occurred in 1936, not to mention neonatal deaths. If we finally conclude that at least half of these are preventable, some effect on maintaining our population balance should result.

Dr. Montgomery has classified stillbirths into groups, in each of which there is a definite factor of preventability: ante-partum syphilis can be effectively treated; pregnancy toxemia is being reduced; birth trauma does not afford a satisfactory picture, it should be much less; placental anomalies cannot be avoided but their handling can and has been improved. It would appear therefore that the principal attack should be made on syphilis, toxemia, and operative delivery. The latter in particular demands our more immediate attention. Have we not, in failing to observe proper indications, to insist on operative deliveries being carried out with competency and under proper environment, contributed to a stillbirth incidence which could be reduced? Dr. Elizabeth Tandy in her study of the subject finds that among one thousand cases of stillbirths distributed among 216 hospitals in which over 23,600 are delivered annually, 62 per cent were delivered spontaneously and 38 per cent by operative procedures. Forceps extractions preceded 35 per cent and were the most frequent, breech extractions were second with 25 per cent, versions accounted for 14 per cent and were third on the list and cesarean sections were fourth with 14 per cent. It was claimed that the fetus was dead before delivery in 73 per cent. One may question this figure but even if accepted as true, it leaves 27 per cent of the fetuses alive before operation was started. One cannot draw final conclusions from 1,000 cases but probably we can multiply these results by 78, for it is estimated that

week. These live births necessarily end fatally in almost every case. At the Lying-in Hospital we practically never save a baby that weighs less than 1,000 gm. That weight is about as near the margin of viability as we can calculate.

The reports of the stillbirth certificates and death certificates of neonatal infants as to the cause of death do not mean a thing unless derived from autopsies, and in many autopsies we were unable to find the cause of death.

TABLE I. CAUSES OF DEATH IN 526 NECROPSIES—245 NEONATAL DEATHS AND 281 STILLBIRTHS

	NEONATAL DEATHS				STILLBIRTHS					
	TOTAL	TERM	PREMATURE	PREVIABLE	TOTAL	TERM	PREMATURE	PREVIABLE	NO.	PER CENT
Malformations	60	43	17	0	35	19	16	0	98	18.1
Hemorrhage*	57	32	23	2	26	20	6	0	83	15.8
Anoxemia	30	9	20	1	67	35	31	1	97	18.5
Infections	11	6	4	1	5	4	1	0	11	2.9
Miscellaneous	9	2	7	0	0	0	0	0	9	1.7
Undetermined	78	11	40	27	148	50	68	30	226	43.0
Total	245	103	111	31	281	128	122	31	526	100.0

*Hemorrhage includes only gross visceral and intracranial lesions.

Of the neonatal deaths, of which there were 245 out of 526 necropsies, malformations played the major role, especially in the term infants. We cannot prevent those deaths. The next largest group in which the cause of death was found was hemorrhage. This group includes all of the visceral hemorrhages and intracranial lesions. In the next group there was anoxemia or evidence of it. Then came infections in which syphilis, though involving only a small group, is included. Then there was the miscellaneous group of cases, especially of the premature infants, in which no pathologic lesion could be found which would account for the death.

The same thing holds true for the 281 stillbirths. Malformations still play the major role; hemorrhages come next; anoxemia plays a greater role than in the neonatal deaths, but the infections play only a small role. There are a large number of term and premature viable and of previable infants in which no demonstrable pathologic lesion could be found to account for the death.

TABLE II. COMPLICATIONS OF PREGNANCY ASSOCIATED WITH NEONATAL DEATHS AND STILLBIRTHS, CHICAGO LYING-IN HOSPITAL, 1931-1938

	LIVE BIRTHS		STILLBIRTHS		TOTAL
	DEATH DUE TO COMPLICATIONS	DEATH NOT DUE TO COMPLICATIONS	DEATH DUE TO COMPLICATIONS	DEATH NOT DUE TO COMPLICATIONS	
Abruptio placentae and placenta previa	25	14	73	5	117
Toxemia	28	16	61	9	114
Abruptio placentae and toxemia	9		19		28
Cord prolapse, etc.	6	4	33	11	54
Medical complications	14	3	8	3	28
Syphilis	2	4	2	5	13
Total	84	41	196	33	354

If these deaths are analyzed from the standpoint of maternal complications, placental causes associated with hemorrhage, such as placenta previa and premature placental separation, are found to be very important factors. Toxemias give even

TECHNIC AND RESULTS OF ROUTINE FETAL ELECTROCARDIOGRAPHY DURING PREGNANCY*

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FETAL electrocardiography is a new method for determining during pregnancy whether or not the fetus is alive. It is the only graphic method yet available for such a purpose; apart from this method we still depend upon the stethoscope and on observations of fetal movements for such information.

In 1933, Steffan and Strassmann published the first fetal electrocardiograms taken on pregnant women, which, in three different external leads, gave definite evidence of action of the fetal heart superimposed on that of the mother.

In 1936, Strassmann gave the first report in this country regarding fetal electrocardiography during pregnancy. At that time, the technic was still in the stage of inception. Positive results had been obtained in only a third of the cases in which these observations were undertaken.

Having been able to identify definitely the fetal heart waves in the electrocardiogram of a pregnant woman, it has been only a matter of improving the technic to increase the percentage of positive results, in order to develop the method for routine purposes. It is one problem to create a new method of diagnosis and another to make such a method practical for routine use. To the latter end, it seemed advisable to keep the following principles in mind:

1. Any modification of the electrocardiographic apparatus which is generally in use was avoided. Changes were necessary, however, in the experimental stage, to obtain positive results. But, for routine purposes, such changes would make the practical use of fetal electrocardiography almost impossible.

2. Unusual leads, such as placing electrodes in the rectum or vagina or on the abdomen were not employed. Such technic would arouse antagonism and objections on the part of physicians and patients. Application of electrodes to extremities is familiar to everybody and, therefore, is preferable in fetal electrocardiography.

3. In spite of these limitations, it was necessary to increase the sensitivity of the test, in other words to increase the amplitude of the various waves. At the same time, it was necessary to decrease the shakiness and fuzziness of our tracings, that is, to cut out, as far as possible, muscular fibrillation and interference from the outside, especially that due to electric current.

*Read at a meeting of the Chicago Gynecological Society, April 15, 1938.
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†Now residing in Houston, Texas.

78,000 stillbirths occur annually in the United States. There probably is little doubt that radical or incompetent obstetrics must be regarded as a definite factor and points the way to the solution of certain phases of the stillbirth problem.

It is to be hoped that the local situation so ably discussed by Dr. Montgomery may lead to similar case finding studies elsewhere. Continuing surveys, critical and informatory, are being initiated in New York City, and other communities should be stimulated to do the same. The New York Department of Health has developed a new form of certificate for all premature interruptions of pregnancy, the more detailed recording of which should in time give us further valuable information. The work of Dr. Montgomery and his Committee in Philadelphia, as well as the other activities referred to, should accomplish much in reducing the wastage of fetal life in this country. Dr. Montgomery's hopeful view that we may look forward to a reduction in fetal deaths is, in my opinion, dependent in large degree upon what the profession will do in exercising its own influence on those preventable factors which we have acknowledged as among the chief causes of stillbirths and neonatal deaths, including syphilis, toxemia, obstetric analgesia, and operative deliveries.

DR. PHILIP F. WILLIAMS, PHILADELPHIA, PA.—We have felt in Philadelphia that we should have studies made on all three types of mortality, not only maternal but also fetal and neonatal. In order to complete the studies the Department of Health has recently organized a Committee which at the present time is using the same cooperative form of study of neonatal deaths.

We have tried to organize in Philadelphia an obstetric staff conference in each hospital. The deaths are referred to these meetings for an opinion, then they go to the respective study committees. In that way each death is referred back to the smallest and nearest component group of physicians who have come in contact with that case. In that way a more detailed and close inspection of the circumstances surrounding the death is brought to light. If we are to effect any further reduction in the death rate it will be done by a more intimate study by the hospital conferences.

thigh. (4) The electrodes then are fastened with bandages 4 inches wide which have been soaked in saturated saline solution. (5) The patient rests ten to fifteen minutes before the electrocardiogram is taken. (6) Tracings are taken with the usual leads (I, II, and III). (7) The electrode is changed from left thigh to right thigh. (8) Tracings then are repeated with Leads II and III (right arm—right thigh, left arm—right thigh, respectively). (9) Two feet of film should be taken for each tracing. (10) Outside disturbances from other electric apparatus should be guarded against.

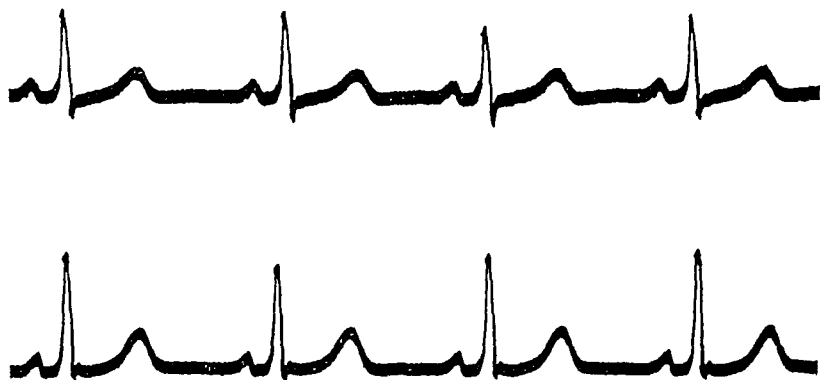


Fig. 1.—Lead I. Upper tracing taken with usual technic; patient in a sitting position. Lower tracing illustrates higher amplitude of waves and quieter zero line than in upper tracing; obtained by special technic, patient in supine position.

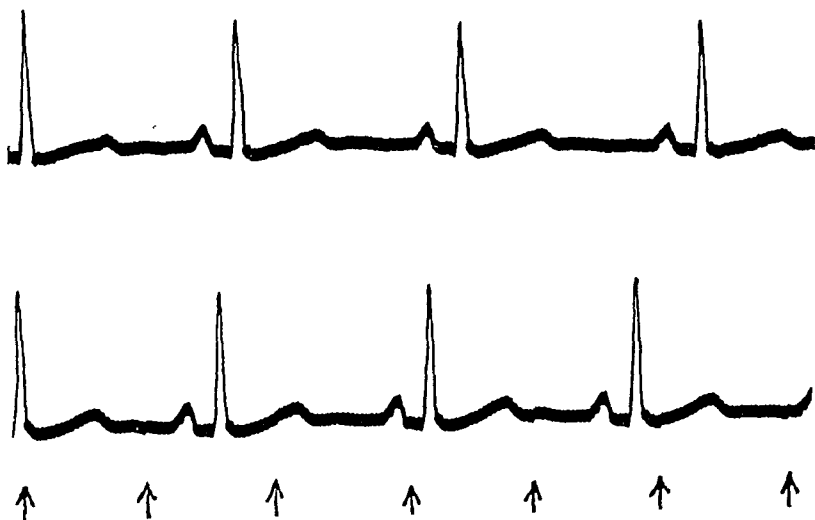


Fig. 2.—Lead II. Upper tracing taken with usual technic. Lower tracing taken with special technic. Fetal waves are indicated by arrows.

To illustrate the importance of the above-mentioned technical procedures, tracings are shown which were obtained on the same patient on the same day by taking the electrocardiograms by the usual technic and then by our special technic (Figs. 1, 2, 3, and 4).

The patient, aged 25 years, had experienced two previous pregnancies. The tracings shown were taken fifteen days before spontaneous delivery of her third child. The top tracings are those taken by the ordinary routine methods in the electrocardiographic laboratory; the bottom tracings were taken by application of our special technic.

The final simple technic was developed on the basis of these three requirements. As is always the case, all kinds of complicated procedures were used before a simple technic was devised.

TECHNIC OF FETAL ELECTROCARDIOGRAPHY

As was expected previously, the routine Leads I, II, and III are fully satisfactory. However, in addition, we take Leads II and III on the right side after moving the electrode from the left thigh to the right thigh. Thus, we obtain a total of five tracings: (1) right arm—left arm; (2) right arm—left thigh; (3) left arm—left thigh; (4) right arm—right thigh; (5) left arm—right thigh.

These five leads cover the main directions the axis of the fetal heart might have in the body of the mother, projected on a two dimensional field. From our practical experience these usually are sufficient. In a three dimensional field, however, the possibilities concerning the direction of the axis of the fetal heart are unlimited. Some of our failures to record fetal components might be owing to this fact.

The electrodes we apply are those used routinely in the electrocardiographic laboratory of the Mayo Clinic. Their size is 6 inches (15.24 cm.) square. But, in contrast with the usual technic, the electrodes are fixed on the upper arm and thigh by bandages 4 inches in width. Previous to application, the bandages are soaked in saturated solution of sodium chloride; also, the skin and electrodes are moistened with the same solution. The reason for using saline solution and for applying the electrodes on the upper part of the extremities is, of course, to lose as little as possible of the fetal cardiac impulses. The nearer the electrodes are situated to the trunk of the body, the less resistance to be overcome.

Instead of saline solution, paste was tried in several cases, but without any advantage. In our particular type of work, use of paste between the skin and electrodes seemed to increase the fuzziness of the tracings, which made identification of the fetal waves more difficult. There does not seem to be much difference between use of saline solution and tap water.

Another difference between usual electrocardiographic technic and this technic concerns the position of the pregnant woman. We do not take the electrocardiogram with the patient in a sitting position. The patient is placed on a couch lying on her back, the head supported by a pillow. She must be absolutely comfortable and relaxed. After applying the electrodes, ten to fifteen minutes are allowed to elapse before starting the test. During this interval, the patient closes her eyes and rests. It is advisable to record 2 feet of film for each tracing. After Leads I, II, and III are taken, the electrode from the left thigh is changed to the right thigh and Leads II and III are repeated.

It is necessary to explain the significance of these procedures. A sitting position always requires some muscular action; this is not true of the supine position. This muscular action does not interfere with routine electrocardiography but it does interfere with fetal electrocardiography. For this same reason, in order to eliminate muscular fibrillation, it is advisable to wait ten or fifteen minutes after application of electrodes before taking the test. There will, of course, be some nervous patients who, in spite of these precautions, will have some muscular fibrillation which causes definite fuzziness of the tracing and makes identification of the fetal waves somewhat difficult.

Another point should be mentioned. Occurrence of disturbances from the outside, especially by other electric apparatus, must be prevented. The shakiness caused by extraneous electric current is easily noticeable on tracings. There may be small waves, regular in size and periodicity, which may not be annoying in routine electrocardiography, but may interfere with identification of fetal waves.

Thus, the main points in our technic of fetal electrocardiography, in short, are: (1) The patient is placed flat on her back on a couch. (2) The skin and the electrodes are moistened with saturated saline solution. (3) The electrodes are placed on the upper arms and left

contains shorter amplitudes and a restless zero line. The lower tracing illustrates the bigger maternal waves, a more restful zero line and in addition, the fetal waves in a most distinct way. There are no fetal waves visible in the upper tracing.

Twelve different patients were examined by electrocardiographic methods, first, in the usual manner and, then, by means of our technic as described above, one test after the other without making any changes in the apparatus. In all 12 cases fetal waves were recorded by means of our special technic. Only 3 of the 12 cases contained evidences of fetal waves when the usual technic was used, but these were less distinct.

Before giving our results there is one more important point, that is, how to read the fetal electrocardiograms, in other words, how to identify the fetal waves. Impulses of the fetal heart are too weak to give in a visible way, with our present technic, the same configuration of heart action that we find in the electrocardiogram of adults. The P- and T-waves do not show up. The R-waves usually are the only visible part of the fetal heart action in tracings taken during pregnancy. Since, in vertex presentation, the fetal heart is upside down in relation to the maternal heart, the fetal R-waves appear as negative waves (deflected

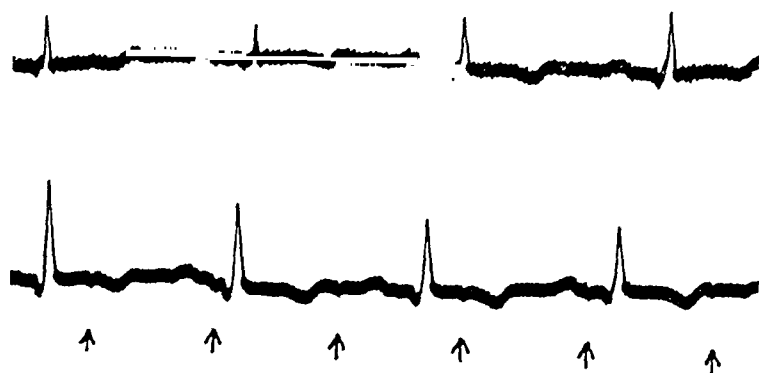


Fig. 5.—Lead III. Upper tracing taken with usual technic; short maternal R-waves and restless zero line. No fetal waves present. Lower tracing taken with special technic contains higher maternal R-waves than in upper tracing. Fetal waves indicated by arrows.

below the zero line), the amplitude of which varies between 1 and 2 mm. They are visible to the naked eye but, occasionally, use of a magnifying glass facilitates identification. In addition to the relatively large negative wave there is often present a short positive wave (deflected above the zero line). In breech presentations, the opposite occurred, that is a diphasic complex with a long positive and a short negative component. Such a positive R-wave is identified with more difficulty than the negative R-wave because, among the positive maternal waves, positive fetal waves do not show up quite as distinctly as do the negative waves that are associated with vertex presentation (see results). The fetal waves occur regularly in a rhythm independent of that of the mother. They are best visible when they appear between the maternal R- and T-waves or between the maternal T- and the following P-wave. When they coincide with the maternal QRS complex or with the T-wave they are hardly visible. The fetal waves have always the same size and form in one tracing and usually the same frequency of occurrence.

Fig. 1 illustrates the first lead (right arm—left arm). As previously mentioned, the first lead usually does not give evidence of fetal action. When the fetus is in a vertical (vertex or breech) position, the axis of the heart is more or less vertical, the isoelectric zones are, therefore, horizontal and parallel to the first lead. However, it is obvious that, owing to our technic, the amplitude of the maternal R- and T-waves is larger than it is in tracings obtained by the usual routine methods and, at the same time, the zero line is quieter. Thus, the main conditions necessary to obtain the fetal waves in the other leads are fulfilled.

In Fig. 2, the upper tracing gives almost no evidence of fetal cardiac action. The lower tracing contains small negative deviations occurring at regular intervals (140 per minute) independent of the rhythm of the maternal waves. These negative waves, indicated by arrows, are the fetal R-waves.*



Fig. 3.—Lead III. Upper tracing, usual technic; no fetal waves. Lower tracing, special technic. Fetal waves are indicated by arrows.



Fig. 4.—Right thigh leads with special technic. Fetal waves present in both tracings; indicated by arrows.

Lead III, illustrated in Fig. 3, usually gives the best results when the fetus is in a vertical position. In the lower tracing one recognizes distinctly the fetal waves, indicated by arrows. The upper tracing does not show the fetal waves at all. In addition, Fig. 4 contains the tracings obtained by Leads II and III taken from the right thigh using our technic. Both leads show the fetal waves distinctly. In all four positive leads, the fetal waves have the same rate, 140 per minute; this was verified by means of the stethoscope.

Fig. 5 illustrates the results obtained in the third lead of another pregnant woman eight days before delivery. The upper tracing taken in the usual manner

*Fetal waves in the original tracings are clearer than in photographs and reproductions.

hand, the diagnosis of breech presentation was made without examining the patient, on account of the positive form of the waves (deflected above the zero line).

The negative electrocardiograms in 5 cases of vertex presentation were mostly early cases. One electrocardiogram was taken forty-seven days before delivery, another thirty-eight days before delivery, and the third thirty-two days before delivery. In taking the fourth, sixteen days before delivery, paste was used instead of saline solution which, as mentioned above, caused more fuzziness in the tracings and made identification of fetal waves impossible. The fifth electrocardiogram, taken ten days before delivery, gave evidence of interference probably owing to muscular fibrillation. The patient was rather nervous.

The closer the patient is to the expected date of delivery, the higher is the percentage of positive fetal electrocardiograms. Table I gives the exact figures. In the last three weeks before the expected term, the highest percentage of positive fetal electrocardiograms occurred. This is especially clear when we consider the cases of vertex presentations only (Table II).

TABLE I. TIME BEFORE DELIVERY FETAL ELECTROCARDIOGRAM TAKEN

DAYS BEFORE DELIVERY	TOTAL ELECTRO-CARDIOGRAMS	RESULTS			
		POSITIVE		NEGATIVE	
		CASES	PER CENT	CASES	PER CENT
0-20	44	40	91	4	9
21-70	26	21	81	5	19
Total	70	61	87	9	13

TABLE II. TIME BEFORE DELIVERY FETAL ELECTROCARDIOGRAM TAKEN. VERTEX PRESENTATIONS

DAYS BEFORE DELIVERY	TOTAL ELECTRO-CARDIOGRAMS	RESULTS			
		POSITIVE		NEGATIVE	
		CASES	PER CENT	CASES	PER CENT
0-20	36	34	94	2	6
21-70	23	20	87	3	13
Total	59	54	92	5	8

Electrocardiograms were not taken before the last two months of pregnancy because we knew from previous experience that under such circumstances, with our present technic, too large a percentage of negative results is to be expected.

It is not proposed to use fetal electrocardiography as another test for pregnancy, but it is proposed that it be employed to determine and study fetal life during the last period of pregnancy, especially in the days preceding and during labor. If a physician should care to use fetal electrocardiography, he should first take tracings only in the last three weeks of pregnancy until he becomes familiar with the method and acquires the ability to read the tracings. The reason for this, as previously stated, is that the closer the patient is to the expected term, the more leads become

A single deviation or several similar deviations spread over the tracing may mean nothing. They may not be true fetal waves especially in fuzzy tracings. *A fetal electrocardiogram must be regarded as positive only if the waves can be followed through the entire tracing and the exact fetal heart rate can be determined.* It is necessary to use a ruler and a divider. With the divider, the distance between two waves that are suspected of being of fetal origin is measured and, using this same measurement an attempt is made to find the same type of wave always at the expected interval. If the fetal wave has been chosen properly, to begin with, such waves will be found present throughout the tracing, disappearing only when maternal waves are superimposed. It is advisable to indicate the fetal waves in ink on the electrocardiogram. After having marked at least ten to twenty consecutive fetal waves the ruler is used to figure the fetal heart rate. One inch of film represents one second; therefore, it is easy to find the fetal rate by counting the number of fetal waves in 3 to 6 inches of film and multiplying it by twenty or ten, respectively. Also, the maternal heart rate always should be determined. There is an interesting relationship between the maternal and the fetal heart rate. It is usually 3:5 or 4:7. The fetal rate is not quite twice as fast as that of the mother. The faster the pulse of the mother the faster is that of the fetus and vice versa. The smaller the fetus, the faster its pulse rate. Therefore, the earlier in pregnancy, the faster the fetal pulse. The relationship between the maternal and fetal heart rate opens a wide field for study, by use of the fetal electrocardiogram under various conditions, especially in labor.

RESULTS

We wish to emphasize again that a fetal electrocardiogram must be regarded as positive only if the fetal waves can be followed through the entire tracing and the exact fetal heart rate can be determined. This is the only way to avoid error. Many waves may be suspected of being of fetal origin but this should not be taken for granted without first having determined their definite rhythm and regular appearance. Our results are based on this principle.

Seventy electrocardiograms were recorded from 52 gravidas using the technic as described above. Sixty-one or 87 per cent were positive fetal electrocardiograms and 9 or 13 per cent were negative. Fifty-nine electrocardiograms were taken in 49 cases of vertex presentation. Fifty-four or 92 per cent of these were positive fetal electrocardiograms and 5 or 8 per cent were negative. Eleven electrocardiograms were taken in 3 cases of breech presentation. Seven or 64 per cent of these were positive fetal electrocardiograms and four or 36 per cent were negative.

The higher percentage of negative electrocardiograms in cases of breech presentation is owing to the fact, mentioned above, that the positive (deflected above the zero line) fetal deviations are recognized with more difficulty (owing to the confusing positive maternal waves) than are negative fetal waves (deflected below the zero line). On the other

It is interesting that the number of positive tracings was highest and almost the same (46 and 45) in the third lead and in the fifth (left arm—right leg). The reason is that of all leads employed these leads are the most favorable for recording impulses from the fetus in left vertex position, and this position occurs more frequently than right vertex position. In the latter position, the second and the fourth leads (right arm—right leg) are the most favorable, corresponding to the axis of



Fig. 6.—Leads II and III taken one day before delivery. Fetal waves indicated by arrows.



Fig. 7.—Right thigh leads; same patient as in Fig. 6. Fetal waves indicated by arrows.

the fetal heart. Therefore, it is not amazing that the incidence of the number of fetal tracings obtained from these two leads is very much the same (29 and 32).

This very fact that two leads are linked together in their positive or negative results also explains the observation that a greater number of electrocardiograms is positive in two or in four leads (31 per cent and 29 per cent, respectively) than in three leads (15 per cent, Table III).

positive in the electrocardiogram. Table III illustrates in how many leads positive fetal electrocardiograms were obtained. Three-fourths of positive fetal electrocardiograms occurred in at least two leads and almost a third of them in four leads.

The relationship between the time before delivery and the number of positive leads is illustrated in Table IV. During the last three weeks before delivery more than twice as many fetal electrocardiograms are positive in four different leads (38 per cent) as occur during the time previous to three weeks before term (14 per cent). The reason for this lies in the fact that the larger the fetus the more its heart action shows up, not only in the favorable leads but also in the others.

TABLE III. POSITIVE FETAL ELECTROCARDIOGRAMS OBTAINED

POSITIVE IN	NUMBER	PER CENT
1 Lead	15	25
2 Leads	19	31
3 Leads	9	15
4 Leads	18	29
Total	61	100

TABLE IV. RELATIONSHIP OF NUMBER OF POSITIVE LEADS TO TIME BEFORE DELIVERY

POSITIVE IN	0-20 DAYS		21-70 DAYS	
	NUMBER	PER CENT	NUMBER	PER CENT
1 Lead	10	25	5	24
2 Leads	11	27	8	38
3 Leads	4	10	5	24
4 Leads	15	38	3	14
Total	40	100	21	100

As an example of a positive fetal electrocardiogram recorded at the end of a full-term pregnancy, tracings of a gravida, aged 20 years, were chosen. The electrocardiogram was taken on Dec. 8, 1937. The following day a female baby who weighed 3,510 gm. was delivered by forceps. The electrocardiogram gives evidence of fetal waves in four leads (Figs. 6 and 7). They are indicated by arrows. The maternal heart rate decreased during the test from 98 to 88; that of the fetus, consequently, decreased from 150 to 144. Not all the tracings, of course, are as clear as this one. Especially, not all leads are equally favorable in the earlier cases. Therefore, it is necessary to mention the value of the various leads that are employed.

In 61 positive fetal electrocardiograms, there were 152 positive tracings. The tracing of the first lead was never positive; the tracing of the second lead was positive in 29 instances; the third in 46; the fourth lead (right arm—right leg) in 32, and the fifth lead (left arm—right leg) in 45 instances. The reason why the tracing of the first lead was never positive has been mentioned above. In longitudinal positions (vertex or breech presentation) the axis of the fetal heart is vertical. Therefore, the iso-electric zones are horizontal and are parallel with the first lead (right arm—left arm). We did not have a case of transverse position of the fetus in our series. In this particular instance, however, the tracing of the first lead might be expected to be positive.

deliveries on May 31, 1935 and July 24, 1936. On Aug. 10, 1935, a large ovarian cyst, 20 by 15 cm. which weighed 1,050 gm. had been removed at the clinic. When she came to the clinic on Dec. 3, 1937, she had all signs of pregnancy but fetal heart tones could not be heard. It was fifty-five days before the expected date of delivery. The fetal electrocardiogram taken on the same day was positive in the third lead (fetal rate 138). Two weeks later, on Dec. 27, 1937 and finally on Jan. 4, 1938, fetal heart tones could not be heard. Electrocardiograms taken on Dec. 15, 1937, and Dec. 27, 1937 were both positive in four leads. A living male baby (3,850 gm.) was born spontaneously on Jan. 14, 1938. The tracings in Figs. 8 and 9 were taken on Dec. 15, 1937, forty-three days before the expected date and thirty days before delivery.

In case doubt exists as to whether the fetus is alive during the last two months of pregnancy, especially if such a doubt arises when the patient is in labor, fetal electrocardiography might be of practical value.

The scientific side of this test opens an even wider field. The only method available for study and observation of the condition of the fetus in pregnancy and labor, up to now, has been that of stethoscopic examination which, of course, for practical purposes will never be replaced. For research work, however, a more accurate test is needed. The fetal electrocardiogram recorded in pregnancy and labor gives us records of documental value, tracings which show the action of the maternal heart and that of the fetus at the same time. The relationship between the circulation of the mother and that of the unborn infant can be studied under various conditions. It is not necessary to repeat what was said about other uses of fetal electrocardiography in the paper given on Dec. 2, 1936.² Fetal electrocardiography is still a new method which can be improved. However, it has possibilities of being of value for practical and scientific purposes.

SUMMARY

The principles on which the routine technic of fetal electrocardiography has been developed are use of the electrocardiographic apparatus without modification, application of electrodes to the extremities only, increase of the amplitude of waves and decrease of the fuzziness of tracings by simple means. The technic of obtaining and interpreting fetal electrocardiograms is described in detail. The difference between the results obtained by use of the usual technic and those obtained by use of special technic is illustrated in Figs. 1 to 3.

Seventy fetal electrocardiograms were recorded from 52 patients during the last seventy days of pregnancy. Sixty-one or 87 per cent of the electrocardiograms were positive and 9 or 13 per cent were negative. During the last twenty days of pregnancy 40 out of 44 electrocardiograms or 91 per cent were positive. Between the twenty-first and seventieth day before delivery 21 out of 26 electrocardiograms or 81 per cent were positive. In cases of vertex presentation, during the last twenty days of pregnancy, 94 per cent of the electrocardiograms were positive and, between the twenty-first and seventieth days before delivery, 87 per cent were positive.

The first appearance of fetal waves usually occurs in that lead which is most parallel with the axis of the fetal heart (25 per cent of positive cases). There is another factor which may explain the higher incidence of fetal waves in Lead III in contrast with Lead II. Examination of the tracings will show that the tracing from the second lead usually has a more fuzzy character than that of the third lead, a factor which makes identification of the fetal waves more difficult in the second lead.

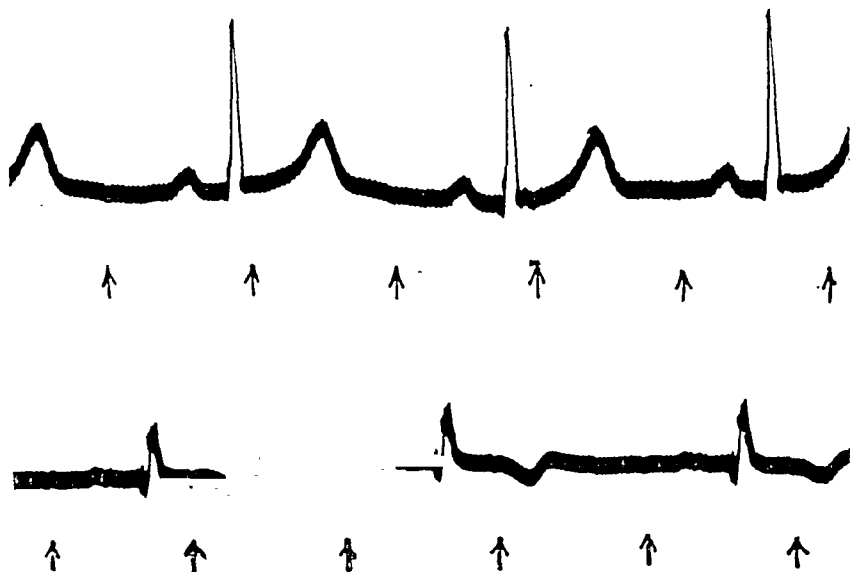


Fig. 8.—Fetal electrocardiogram taken forty-three days before term, thirty days before delivery. Fetal heart tones not heard through stethoscope. Fetal waves in Leads II and III indicated by arrows.

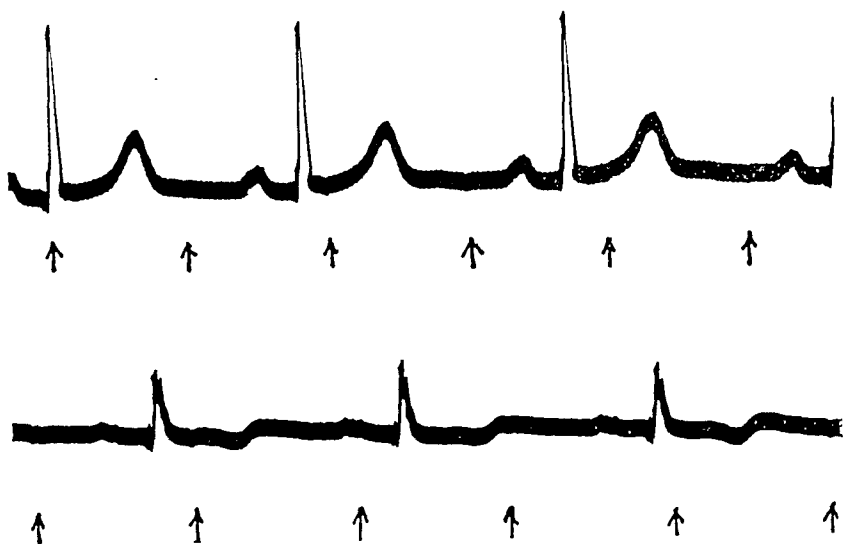


Fig. 9.—Right thigh leads; same patient as in Fig. 8. Fetal waves indicated by arrows.

Having reported the technic and results of fetal electrocardiography we should discuss the value of this test. There is a practical and a scientific side to every medical method. The practical value of the fetal electrocardiogram can be illustrated best by report of a case in our series.

The patient, aged 27 years, weight 179¾ pounds (81.6 kg.), had her last menstrual period on April 20, 1937. She was a para ii, having had two spontaneous

THE RELATION OF BASAL BODY TEMPERATURE TO FERTILITY AND STERILITY IN WOMEN

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PERIODS of fertility and sterility undoubtedly occur during the menstrual cycle in the human female. These have been explained on theories for each of which some inadequacy must be admitted even with the most careful application of the principles embodied.

In this essay we present data which offer a practical method for the regulation of conception in fertile women. They may also be valuable in the study of women who are reputedly barren.

In the newer experimental approach to the subject of human ovulation many methods have been investigated. Most of these are in fair agreement. Some methods, however, are unsuitable for determining the day of rupture of the ovarian follicle and, in all, the difficulty of forecasting variability has been the chief handicap to practical application.

In the older literature pregnancy has been reported by different observers to result from exposure on nearly every day of the menstrual cycle. As late as 1927 Dickinson³ made an exhaustive survey of existing data and came to the conclusion that unexpected variability in ovulation constitutes a major hazard to estimation of temporary sterility by any set rule of thumb. At the very date of publication of Dickinson's conclusion there were in progress two investigations which have considerably clarified the dating of human ovulation.

Ogino,^{14, 15} following the method of L. Fraenkel,⁶ made an estimate of the ovulation date in the menstrual cycle by inspecting the ovaries in 83 laparotomies. He claimed a fertile period lasting from the nineteenth to the twelfth day before the oncoming menstrual period. This is not far from Fraenkel's observations published nineteen years previously (1911), although Ogino advocated a relationship of ovulation to the following, not to the preceding, menstruation.

Knaus¹² investigated the reactivity of the uterus to pituitrin and found that the human uterus contracts vigorously up to a date near the middle of the menstrual month when it suddenly becomes almost unresponsive. From existing experimental data he reasoned that corpus luteum inhibition produces the falling off in response and that since the corpus luteum requires about two days after rupture of the ovarian follicle to produce its effect, ovulation must have occurred two days before the negative response is observed. Knaus emphasized the correlation between ovulation thus determined and the oncoming menstruation, claiming ovulation on the fourteenth day preceding menstruation.

Hartman^{7, 8} studied the time of ovulation in the macaque by rectal palpation of the uterus and ovaries, confirming his observations by laparotomy. He further extended his investigation by securing pre-arranged conceptions and recovered embryos of known age from precise dating of fertilization. Subsequently he published a comprehensive critique of all the available data up to 1936. In this contribution⁹ he set down a review of his own data placing ovulation in the female macaque between the eighth and twenty-first days of the cycle. He is unwilling

Besides the usual Leads I, II and III, two more leads were used (right arm—right thigh; left arm—right thigh). The largest number of positive results were obtained in the third lead (46) and in the fifth lead (left arm—right thigh) (45) because they are most favorable in the left vertex position of the fetus which is the most frequent position.

Twenty-five per cent of the positive fetal electrocardiograms were positive in only one lead, 31 per cent in two leads, 15 per cent in three leads and 29 per cent in four leads. In the last three weeks before delivery, 38 per cent of the tests were positive in four leads.

As an example of the practical value of the fetal electrocardiogram, a case is described and the electrocardiogram is shown in which the fetal heart tones could not be heard through the stethoscope and the electrocardiogram gave evidence of a living fetus fifty-five, forty-three, and thirty-one days before the expected term.

Fetal electrocardiography in pregnancy and labor gives objective graphic evidence regarding the viability of the fetus. This is of practical value in doubtful cases in which the older subjective methods, stethoscopic examination, and observation of fetal movements fail. By means of the technic presented, the rate, rhythm, and regularity of fetal heart action can be observed in the electrocardiogram. The scientific field of fetal electrocardiography might even be wider. Such a procedure renders possible observation of the fetus objectively under various conditions in pregnancy and labor. The relationship between maternal and fetal heart action can be easily studied.

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The author reports a case which definitely proves the longevity of spermatozoa. A sterile young woman anxious to bear children had an artificial insemination performed on the twenty-sixth day of the menstrual cycle, hence during a period of physiologic sterility. She menstruated normally two days later and following this abstained from coitus. She did not menstruate after this and subsequent examinations revealed a pregnancy the duration of which coincided with the menstrual history. Evidently in this case the spermatozoa had remained alive and capable of fertilization in the Fallopian tube until an ovum was liberated. Hence, it is possible for spermatozoa to retain their vitality for at least fifteen days. This fact speaks against the principles laid down by Ogino and Knaus concerning the physiologically sterile period.

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that symptoms may appear over a period of three days, these symptoms usually being more pronounced in those women who have had some inflammatory process in the uterus or oviducts. Rupture of the follicle may actually be felt by the woman after careful observation of her own temperature curve.

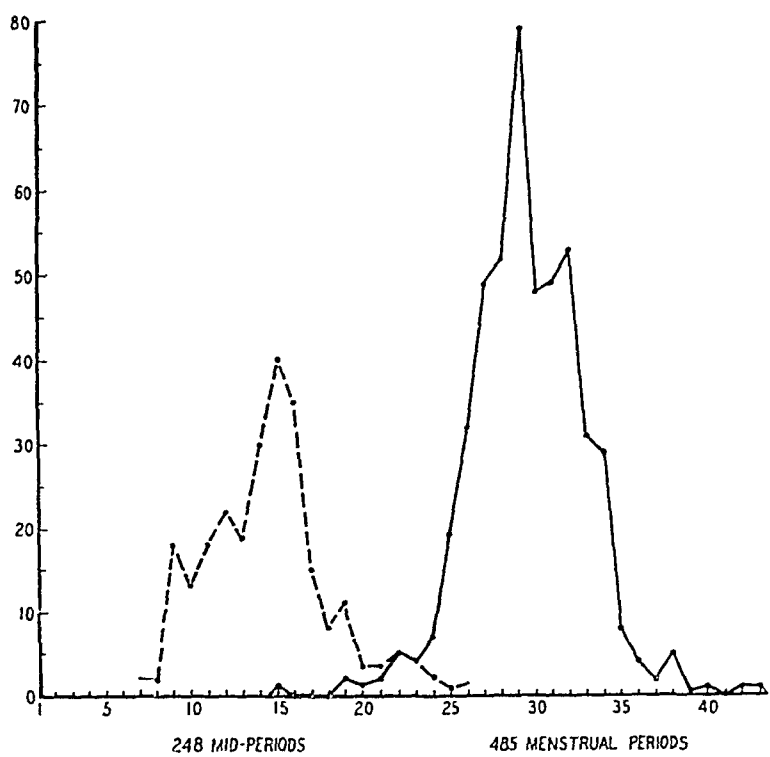


Fig. 1.—The incidence of the midperiod and duration of menstrual cycle. The majority of ovulations indicated by this determination of the midperiod falls between days nine and nineteen of the menstrual cycle with the highest incidence occurring on days fourteen, fifteen, and sixteen.

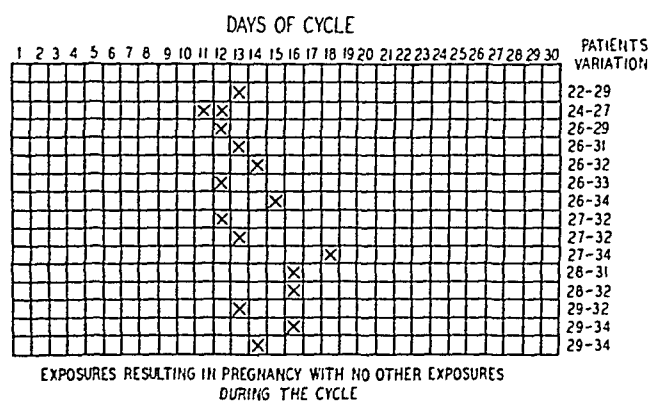


Fig. 2.—Sixteen planned pregnancies successfully started by using midperiod symptoms as indicative of ovarian follicle rupture.

A summary of the menstrual cycles and the observed midperiods is given in Fig. 1. It will be seen that the conformation of the curve of menstrual cycle is very similar in our group to that surveyed by Engle and Shelesnyak⁴ in 1934 and by others. The menstrual cycles in our women, whose ages range from twenty-five to thirty-six years, are very much more regular than those reported in younger women by Engle

to accept the narrowness of span of fertility as advocated by the Ogino-Knaus law, but is quite convinced that a safe period does exist especially during the last quarter of the menstrual cycle.

The data collected by Papanicolaou¹⁶ by the vaginal smear method indicate that in some women it is possible to determine ovulation within a span of two or three days. This information shows the highest number of ovulations to occur on days eleven, twelve, and thirteen with a range from days seven to seventeen. This method has both clinical and experimental application.

Studies by microscopic section of uterine mucous membrane as reported by Schroeder¹⁸ distinguish between nonsecretory (preovulatory) and secretory (post-ovulatory) phases of the mucous glands in the endometrium. Evaluation by this method is in keeping with the theory that ovulation occurs between the fourteenth and sixteenth days of the cycle. This method has been opposed by Evans and Swezy,⁵ the objection being that it is unreliable but Hartman^{9, 10} defends it lending support from his observations on macaques.

Recently Burr, Hill and Allen¹ have applied the principle of electrical potential change to the study of follicle rupture and have been able to record showers of impulses of nervous origin at the time of ovulation in rabbits and more recently² also in women.

In the effort to obtain further information on human ovulation, I began, in 1930, to collect instances of carefully recorded coital exposure which resulted in pregnancy. By establishment of a special "cooperative" clinic at the Maternal Health Association of Cleveland, Ohio, I enlisted the assistance of young women planning pregnancy and willing to serve in an experiment in which the time of the midperiod could be determined.

For several years the women were instructed to keep menstrual records and note particularly signs of the midperiod (*Mittelschmerz*). On the basis of their cycles and midperiods thus defined, exposures were permitted often for a period of several months during what we believed to be the sterile days of the cycle, then a single exposure at the midperiod when we believed conception possible. The results from this experiment emphasized the need for more precise determination of the time of ovulation. Commencing in 1935 morning rectal temperatures were also taken by the women, and since then this has been a routine procedure.

In the early years of our experiment we accumulated information on the duration of the menstrual cycle in the women under observation and recorded their ability to distinguish midmenstrual signs which might be indicative of ovulation. We learned that the signs associated with ovulation are extremely varied and in many women are not recognizable. However, in some women there are definite sensations which, if recorded on the menstrual calendar, can be considered to date the ovulation. This is borne out by the fact that in 15 women, a single exposure at the time of subjective sensation has resulted in pregnancy. The sensations range from a slight temporary discomfort on one or other side of the lower abdomen to severe pain lasting for several hours. In some women there is a vaginal discharge at the midperiod, lasting from one to three days, and there may also be a small amount of bleeding. In one woman there was a regular one-day diarrhea at this time and in several others there were headache and sleeplessness. It seems evident

Fig. 3 shows six successive menstrual cycles in one woman whose temperature curve presents a midperiod low level ascertained to coincide with ovulation through the occurrence of pregnancy from exposure at this precise date and this date only. In this woman, after pregnancy started, there was a fall of temperature at about the time of the expected ovulation of the succeeding cycle. Of 20 women whose pregnancies were planned from the temperature curve (Fig. 4), two, of whom this is one, showed a temperature drop at the first midperiod date after commencement of pregnancy. In the other 18, the temperature remained continuously between 98.5° and 99.5° F. after conception. From

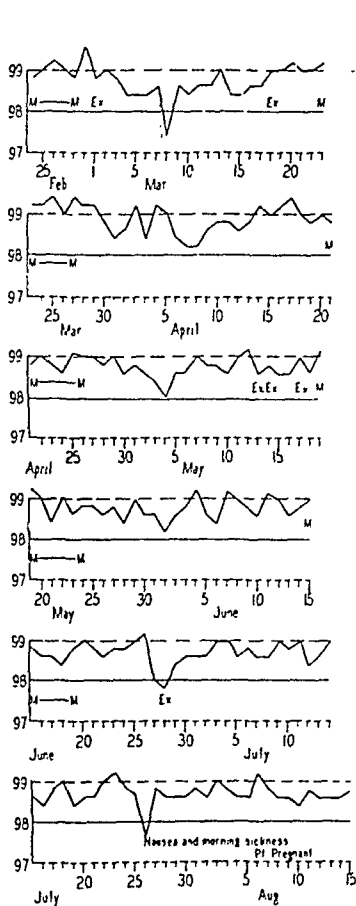


Fig. 3.

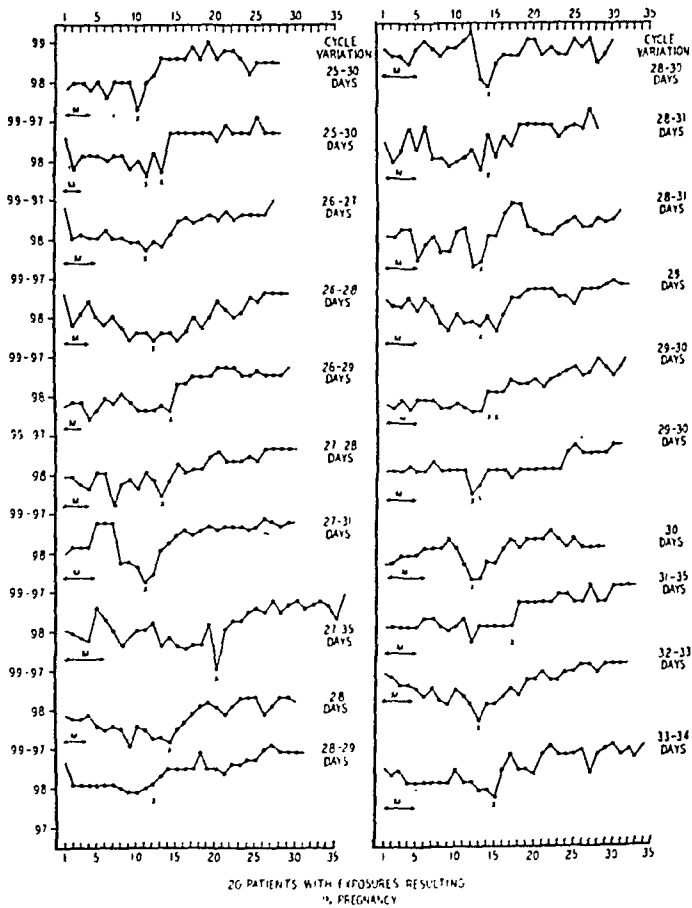


Fig. 4.

Fig. 3.—Six successive menstrual cycles in one woman whose temperature curve presents a midperiod low level ascertained to coincide with ovulation through the occurrence of pregnancy from exposure at this precise date and this date only.

Fig. 4.—The record of the last menstrual cycle in each of twenty women to illustrate the identification of ovulation with the approximate date of the midperiod low temperature. The date of exposure is marked by a cross and the duration of menstruation by a double-headed arrow.

the records of these two women one may hazard the suggestion that when nausea occurs it starts at the date of the midperiod following conception.

Fig. 4 gives the record of the last menstrual cycle in each of 20 women to illustrate identification of ovulation with approximate date of the midperiod low temperature. No pregnancy occurred before the tenth day or after the twentieth day of the cycle regardless of cycle

and Shelesnyak. This is a fairly well-recognized stability that takes place within the older age group of which this evidence is an example. Our women are all married and living with their husbands. Many have had one or more children. There has been no selection on the basis of economic status. A midperiod indication is claimed by about 50 per cent of the women in our group and varies with the length of the cycle.

Fig. 2 shows the range in day of exposure in 16 planned pregnancies successfully started by using midperiod symptoms as indicative of ovarian follicle rupture. There were no exposures during the cycle other than those indicated and no subsequent exposures until after pregnancy had been proved. It will be noted that no pregnancy occurred before the eleventh day of the cycle nor after the eighteenth day regardless of cycle length. It is important to note that pregnancy never occurred at any other date of the menstrual cycle despite exposures permitted in previous months during the assumed sterile days.

Although the midperiod determination yielded interesting data, it is not a method of precision.

Our next step was the recording of early morning rectal temperature in the hope of more accurately dating ovulation, for Van de Velde¹⁹ in 1904 reported variations in body temperature during the menstrual cycle and in 1929 confirmed his observations by supplemental data.²⁰

Further information is essential because of occasional irregularities found in the cycles of all women. Harvey and Crockett¹¹ had already reported in 1932 the temperature record of one woman. Dr. Rubenstein, carrying on a parallel investigation in this laboratory, has recorded routine daily temperatures on a group of women and has recently published his findings.¹⁷

In arranging for single exposure pregnancies one must have ascertained the approximate ovulation date; even then, as is shown in our records of 81 women, pregnancy may not occur until after several timed exposures. The rhythmic rise and fall in the twenty-four-hour temperature record is an established fact, the lowest point being reached usually in the early morning. To standardize the procedure our women recorded their rectal temperature each morning before rising. This routine was carried out at approximately the same time every day. The temperatures were read and recorded to tenths of a degree. When these temperature records are plotted, the resulting curve usually shows that just before menstruation begins there is a slight fall in the temperature which, in most women, reaches 98° F. This level is maintained during the period of flow. At the end of the period there may be a temporary lowering of the temperature which then rises to somewhat above 98° before falling abruptly to reach its lowest level at the midperiod when it may descend to 97° or even lower. After this fall the temperature rises to a level usually above 98° F. and remains practically stationary until the onset of the next menstrual period. This phase is usually regarded as the lutein phase. It is true that not all menstrual cycles show these clear-cut variations, but in the 67 women studied this variation was characteristic of more than 80 per cent of the menstrual cycles.